2014 International Symposium for Recent Advances in Cancer, The 11th Symposium of the Frontiers of Biomedical Sciences and 13th Cross-Strait Symposium on Biomedical Research

June 27-28

Venue

-United Medical Back Building, 16F Lecture Hall, Taipei Medical University

Organized by

-Taipei Medical University

-Taipei Professor Jung-Yaw Lin Academic Education Foundation

Supported by

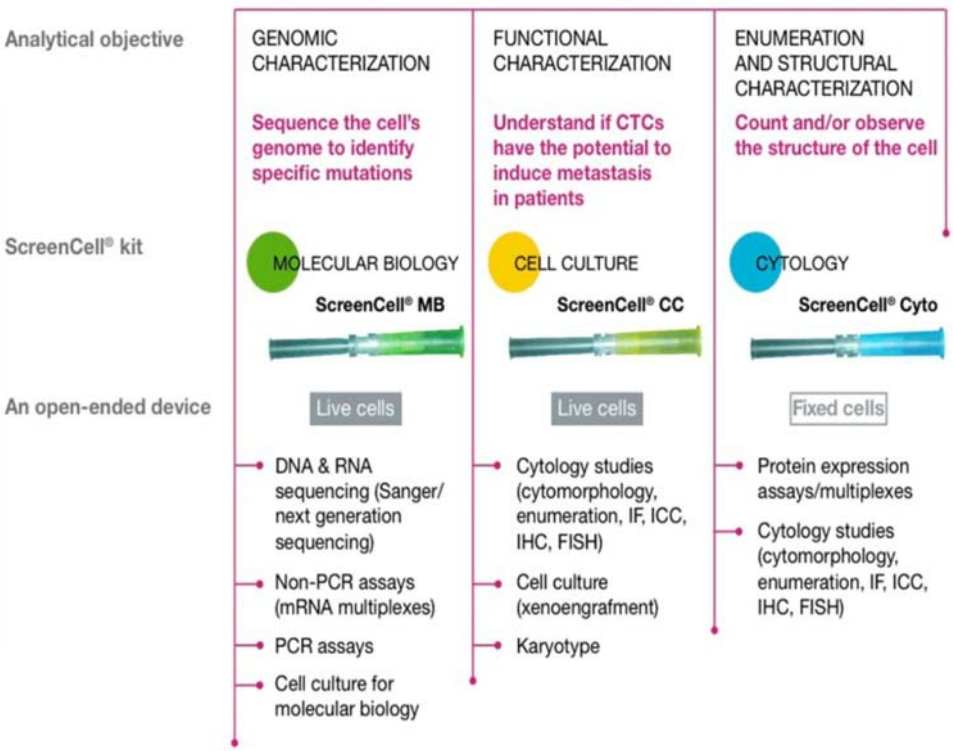
-Ministry of Science and Technology
-Ministry of Education
-Ministry of Foreign Affairs
-Ministry of Health and Welfare
-Introduction of Biomedical Technology and Device Research Laboratories, Industrial Technology Research Institute
-Institute of Biological Chemistry, Academia Sinica
-Department of Health, Taipei City Government
-Department of Information and Tourism, Taipei City Government
-Office of Research and Development, Taipei Medical University
-Core Facility Center, Taipei Medical University

從血液中分離、計數以及取得活循環腫瘤細胞的最佳工具:Circulating Tumor Cells Isolation Kit

監測癌症-就像抽血檢驗一樣簡單!!!

ScreenCell® 分離 CTCs系統

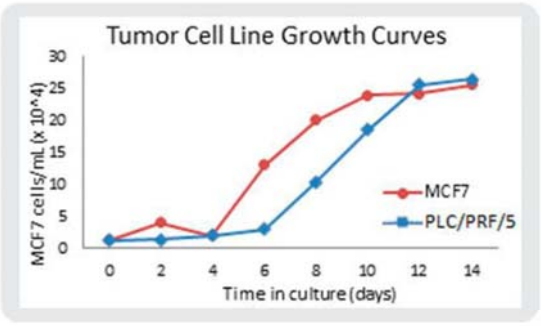
- ✓完全不需任何儀器設備
- ✓可以直接在clinical site 進行採樣分離
- ✓可相容於標準化 IVD 分析法或平臺
- ✓只需 3 分鐘即完成細胞分離
- ✓可分離獲得活細胞以及固定的細胞
- ✓不須依賴任何細胞表面抗原或使用任何抗體，如 EpCAM



ProMab Biotechnologies, Inc

癌症幹細胞分選與增殖培養專用無血清配方培養基

- 專為 Cancer Stem Cells 的培養與選殖所設計的無血清配方培養基。
- 最適合 *Tumor Sphere forming CSC populations* 的生長與選殖。
- 已有多種來源的癌症幹細胞經過測試可於 Cancer Stem Premium™ medium 中生長並形成 Tumorspheres。
- *Ready-to —use (100ml and 500ml)*

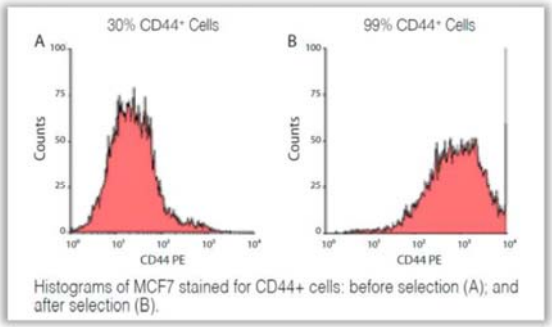


癌症幹細胞分選套組

自腫瘤細胞及組織中鑑別與分離出腫瘤幹細胞，可以提供非常有價值的細胞分布情形，用以研究癌症幹細胞的起源，以及相較於正常細胞，癌症幹細胞形成、維持與分子變異的機制。

我們的癌症幹細胞分離試劑盒提供了對分離特定細胞的完美方法。

Markers	Purity of recovered
$CD24^{-/low}$ $CD44^{+}$	90%-99%
CD24	90%-99%
CD44	90%-99%
CD133	97%-99%
CD326 Epcam	Up to 80%



Histograms of MCF7 stained for CD44+ cells: before selection (A); and after selection (B).

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2014 International Symposium for Recent Advances in Cancer, The11th Symposium of the Frontiers of Biomedical Sciences and 13th Cross-Strait Symposium on Biomedical Research

2014 國際癌症新知研討會、第11 屆前瞻生物醫學科學新知研討會暨第 13 屆海峽兩岸生物醫學研討會

Jun. 27~28, 2014
Taipei Medical University
Taipei, Taiwan

Organized by

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Taipei Medical University (TMU)

Taipei Medical University (TMU), formerly known as Taipei Medical College (TMC), was founded on June 1, 1960 by Dr. Shui-Wang Hu, Dr. Cheng-Tien Hsu and other medical professionals and devoted educators. TMU is located on Wuxing Street in eastern Taipei.

Most of more than 30,000 TMU graduates serve in medical institutions and clinics, while many others are prominent figures in the fields of research, politics, and business. TMU has 7 colleges, 12 undergraduate schools and 14 graduate institutes as well as three affiliated hospitals - TMU Hospital, Wan Fang Hospital, and Shuangho Hospital. With approximately 3,000 beds, TMU is one of the largest health care systems and offers top-quality teaching, research and clinical services in the Taipei metropolitan area. We work continuously to improve the quality of teaching, research and clinical services with the goal of becoming a fully internationalized university that ranks in the top tier worldwide.

Taipei Medical University Hospital

Taipei Medical University Hospital (TMUH) has been serving Taipei for thirty years. Conveniently located near Taiwan's landmark Taipei 101 tower, TMUH offers a warm atmosphere and friendly environment as well as world-tier medical equipment, top-quality medical personnel and patient-centered service. The mission of TMUH encompasses education, research and service through innovation, excellence and commitment to life.

We provide our international friends the same high-quality, efficient and accessible medical services. Our steps toward becoming an internationalized medical center include overseas emergency medical transportation, educational exchanges and medical missions. In addition, we help expatriates in Taiwan with quick and convenient medical services and provide assistance for overseas medical activities, collaborating with the government in expanding medical diplomacy as well as setting up a global network of medical contacts.

Taipei Medical University Wan Fang Hospital

Wan Fang Medical Center dedicated to serving the surrounding area, and is committed to community health promotion. Built in 1989, the Wan-Fang Hospital is the first hospital owned by Taipei City government while run by civilians. In 1998, it passed the Regional Hospital Accreditation and was awarded the international quality certificate of ISO-9002. In 2006, it was awarded the Joint Commission International (JCI) Accreditation. It is the Affiliate Hospital of Taipei Medical University and includes 42 integrated departments of medicine.

Taipei Medical University Shuang Ho Hospital

Shuang Ho Hospital opened on July 1, 2008, with 1580 beds. It is the largest hospital in Taipei County, but also forms a medical “golden triangle” with the Taipei Medical University Hospital and Wan Fang Medical Center, giving a total capacity of over 3000 beds.

Shuang Ho Hospital focuses on providing emergency and critical care, as it is responsible for first response for Taipei County as the only hospital with a medical helicopter and landing pad. Shuang Ho also has the largest dentistry department, with general and family dentistry and six additional specialized clinics. The hospital has the nation's first disabled patient oral health care center to serve the more than 130,000 disabled people in Taipei County. The Kidney Dialysis Center's method of isolating beds, equipment and sections leads the nation in reducing hepatitis C infection. The hospital plans further expansion in the areas of cancer treatment, neurology, minimally invasive surgery, optometry and vision science, health management, cardiology, rehabilitation, trauma surgery and international medical care.

Dear colleagues and friends,

On behalf of Taipei Medical University (TMU), we are delighted to welcome you to participate in the coming joint conference of "2014 International Symposium for Recent Advances in Cancer (ISRAC), The 11th Symposium of the Frontiers of Biomedical Sciences and 13th Cross-Strait Symposium on Biomedical Research" which will be held on June 27-28, 2014 at Taipei Medical University (TMU), Taipei, Taiwan. The conference will be a forum for cancer researchers from universities and research institutes around the world to exchange and discuss their recent discoveries and most updated scientific information. There will be five themes for this conference, including Chromosome Instability in Cancer Development, Niche Environment in Cancer Development, Biomarker and Individualized Therapy in Cancer, Stem Cell Research in Cancer, and Translational Medicine in Cancer.

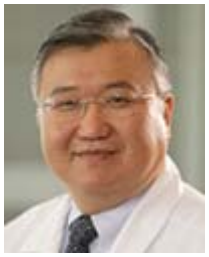
We would like to express our sincere thanks to all, and poster presenters to share with us the recent progress of their research and medical applications in this fast growing field of cancer research at this meeting. I hope that the work presented at this meeting will bring you recent advances in cancer research and medicine, and that each one of you will find the lectures at this meeting useful to your future research. At last, we would like to thank the sponsors, organizing committee members, and volunteers of this meeting for their valuable contributions to this workshop. We hope that your experience at this conference is valuable and memorable.

Thank you again for your participation, and we look forward to seeing you in Taipei Medical University.

Yours sincerely,

Jung-Yaw Lin, Ph. D.
Chair,
2014 ISRAC Conference Committee
Academician, Academia Sinica
Emeritus Professor
Department of Biochemistry
National Taiwan University
Taipei, Taiwan

Wen-Chang Chang, Ph. D.
Co-Chair,
2014 ISRAC Conference Committee
Academician, Academia Sinica
Distinguished Professor
Graduate Institute of Medical Sciences
Taipei Medical University
Taipei, Taiwan



Yun Yen, MD. Ph. D.
Local Organizer,
2014 ISRAC Conference Committee
President and Distinguished Professor
Taipei Medical University
Taipei, Taiwan

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Schedule at a Glance

6/27 Day 1 (Fri.)		
08:30~16:40	**Registration**	**16F**
09:00~09:15	**Opening Remarks**	**16F**
	Conference President — Jung-Yaw Lin, Ph.D. (林榮耀院士)	
	Conference Co-President — Wen-Chang Chang, Ph.D. (張文昌院士)	
	Conference Local Organizer — Yun Yen, M.D., Ph.D. (閻雲校長)	
	Session I: Chromosome Instability in Cancer Development (I)	**16F**
	Moderator: Yun Yen, M.D., Ph.D. (閻雲校長)	
	Distinguished Professor and President, Taipei Medical University, Taiwan	
09:15~09:45	**Edward J. Benz, Jr., M.D.**	
	Toward high precision cancer medicine: lessons learned	
	Academician, United States National Academy of Sciences	
	President and CEO, Dana Farber Cancer Institute; Professor, Department of Medicine, Harvard Medical School, USA	
09:45~10:15	**JoAnne Stubbe, Ph.D.**	
	Radicals your life is in their hands: ribonucleotide reductases as a paradigm	
	Academician, United States National Academy of Sciences	
	Professor, Department of Chemistry, Massachusetts Institute of Technology, USA	
10:15~10:35	**Coffee Break**	**16F/B1**
	Moderator: Wen-Chang Chang, Ph.D. (張文昌院士)	
	Academician, Academia Sinica, Taiwan	
	Distinguished Professor, Graduate Institute of Medical Sciences, Taipei Medical University, Taiwan	
10:35~11:05	**Wen-Hwa Lee, Ph.D. (李文華院士)**	
	Targeting tumor suppressor networks for therapeutic application	
	Academician, Academia Sinica, Taiwan	
	Professor and President, China Medical University, Taiwan	
11:05~11:35	**Ying Huang, Ph.D. (黃昊研究員)**	
	Structural studies of Rhino protein in piRNA biogenesis	
	Professor, Shanghai Institute of Biochemisrty and Cell Biology, Chinese Academy of Sciences, China	
11:35~12:05	**Jingyi Hui, Ph.D. (惠靜毅研究員)**	
	The RNA-binding protein QKI suppresses lung cancer-associated aberrant splicing	
	Professor, Shanghai Institute of Biochemisrty and Cell Biology, Chinese Academy of Sciences, China	
12:05~12:15	**Group Photography**	**1F**
	Outdoor Plaza	
12:15~13:50	**Lunch/ Poster Presentation**	**4F/B1**
	Session II: Cancer Metabolism and Signaling	**16F**
	Moderator: Andrew H.-J. Wang, Ph.D. (王惠鈞院士)	
	Academician, Academia Sinica, Taiwan	
	Distinguished Research Fellow, Institute of Biological Chemistry, Academia Sinica, Taiwan	
13:50~14:20	**Anning Lin, M.D., Ph.D. (林安寧教授)**	
	Computational modeling of IKK signaling	
	Professor and Director, Shanghai Institute of Biochemisrty and Cell Biology, Chinese Academy of Sciences, China	

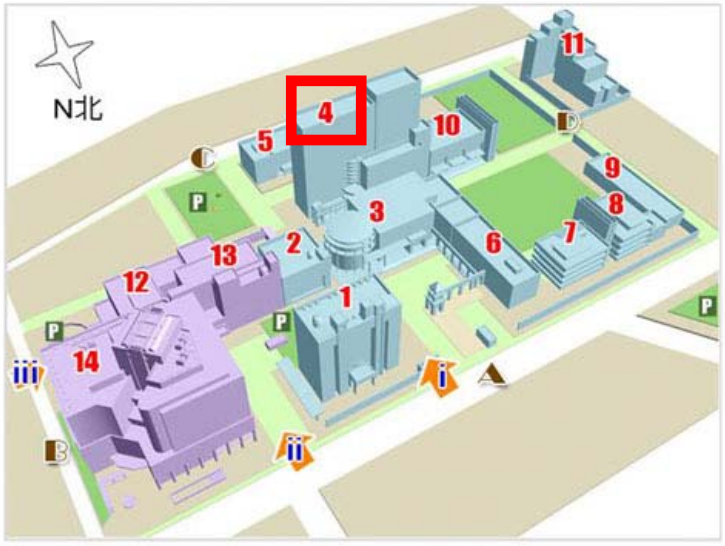
14:20~14:50	**Hsing-Jien Kung, Ph.D. (龔行健院士)** **Metabolism and cancer therapeutics: targeting arginine addiction of cancers** *Academician, Academia Sinica, Taiwan* *President and Distinguished Investigator, National Health Research Institute, Taiwan* **Moderator: Wan-Wan Lin, Ph.D. (林琬琬所長)** *Professor and Director, Graduate Institute of Medical Sciences,* *Taipei Medical University, Taiwan*	
14:50~15:20	**Stephen B. Gruber, M.D, Ph.D., MPH.** **Molecular pathways and survival in colorectal cancer** *Director, Norris Comprehensive Cancer Center, University of Southern California, USA*	
15:20~15:50	**Eva Y.-H. P. Lee, Ph.D. (潘玉華院士)** **Genetic and hormonal contribution in breast cancer: tissue-specific tumor suppression by BRCA1** *Academician, Academia Sinica, Taiwan* *Professor, Basic Science Director, Dept. of Biological Chemistry* *& Dept. of Developmental and Cell Biology, University of California, Irvine, U.S.A.*	
15:50~16:10	**Coffee Break**	**16F/B1**
	Session III: Biomarker and Individualized Therapy in Cancer **Moderator: Yau-Huei Wei, Ph.D. (魏耀揮校長)** *Professor and President, Mackay Medical College, Taiwan*	**16F**
16:10~16:40	**Yu, Alice Lin-Tsing, M.D., Ph.D. (陳鈴津教授)** **Cancer immunotherapy targeting tumor-associated glycans** *Distinguished Chair Professor, Center of Stem Cells and Translational Cancer Research,* *Chang Gung Memorial Hospital and Chang Gung University, Taiwan*	
16:40~17:10	**Hongbin Ji, Ph.D. (季紅斌研究員)** **YAP inhibits squamous transdifferentiation of Lkb1-deficient lung adenocarcinoma through DNp63 repression** *Professor, Shanghai Institute of Biochemisrty and Cell Biology,* *Chinese Academy of Sciences, China* **Moderator: Jing-Jer Lin, Ph.D. (林敬哲教授)** *Professor and Director, Graduate Institute of Biochemistry and Molecular Biology,* *National Taiwan University, Taiwan*	
17:10~17:40	**Min-Liang Kuo, Ph.D. (郭明良教授)** **A novel therapeutic target for treating hepatocellular carcinoma by suppression vascular invasion and metastasis** *Professor and Director, College of Life Science, National Taiwan University, Taiwan*	
17:40~18:10	**Ronggui Hu, Ph.D. (胡榮貴研究員)** **Iron metabolism regulates p53 signaling through direct heme-p53 interaction and modulating localization, stability and function of p53** *Professor, Shanghai Institute of Biochemisrty and Cell Biology,* *Chinese Academy of Sciences, China*	
18:30~20:30	**Banquet**	
08:00~18:00	**Exhibition**	**1F, 16F, B1**

6/28 Day 2 (Sat.)		
08:30~16:40	**Registration**	**16F**
	Session IV: Chromosome Instability in Cancer Development (II)	**16F**
	Moderator: Mien-Chie Hung, Ph.D. (洪明奇院士) *Academician, Academia Sinica, Taiwan* *Professor and Chair, Department of Molecular and Cellular Oncology,* *MD Anderson Cancer Center, The University of Texas, USA*	
08:50~09:20	**Astrid Gräslund, Ph.D.** **Ribonucleotide reductase- a dimetal/tyrosyl free radical enzyme** *Academician, Royal Swedish Academy of Sciences* *Chairman, Dept. of Biochemistry and Biophysics, Stockholm University, Sweden*	
09:20~09:50	**K. Kristoffer Andersson, Ph.D.** **Studies of the NrdF-NrdI complex and different metal ion clusters in class I ribonucleotide reductases** *Professor, Department of Biosciences, University of Oslo, Norway*	
09:50~10:10	**Coffee Break**	**16F/B1**
	Moderator: Jung-Yaw Lin, Ph.D. (林榮耀院士) *Academician, Academia Sinica, Taiwan* *Emeritus Professor, Department of Biochemistry, National Taiwan University, Taiwan*	
10:10~10:40	**Ming-Daw Tsai, Ph.D. (蔡明道院士)** **Structural approach to tumor suppressors and cancer signaling** *Academician, Academia Sinica, Taiwan* *Distinguished Research Fellow and Director, Institute of Biological Chemistry,* *Academia Sinica, Taiwan*	
10:40~11:10	**Hai Jiang, Ph.D. (姜海研究員)** **Probing drug vulnerability associated with recurrent cancer genetic lesions** *Professor, Shanghai Institute of Biochemisrty and Cell Biology,* *Chinese Academy of Sciences, China*	
11:10~11:40	**Zee-Fen Chang, Ph.D. (張智芬教授)** **Ribonucleotide reductase promotes the progression of genome instability via dUTP-mediated replication stress** *Professor and Director, Institute of Biochemistry and Molecular Biology,* *National Yang-Ming University, Taiwan*	
11:50~13:25	**Lunch**	**4F**
	Student Forum 14 位: 6 min/位 **Moderator:** **Yau-Huei Wei, Ph.D. (魏耀揮校長)** *Professor and President, Mackay Medical College, Taiwan*	
	Jung-Yaw Lin, Ph.D. (林榮耀院士) *Academician, Academia Sinica, Taiwan* *Emeritus Professor, Department of Biochemistry, National Taiwan University, Taiwan*	
	Jacqueline Whang-Peng, M.D. (彭汪嘉康院士) *Academician, Academia Sinica, Taiwan* *Superintendent, Taipei Medical University Taipei Cancer Center, Taiwan*	
	Session V: Stem Cell Research in Cancer	**16F**
	Moderator: Hua-Lin, Wu, Ph.D. (吳華林教授) *Professor, Department of Biochemistry and Molecular Biology, College of Medicine,* *National Cheng-Kung University, Taiwan*	
13:25~13:55	**Yun Zhao, Ph.D. (趙允研究員)** **Decoding Ci: from partial degradation to inhibition** *Professor, Shanghai Institute of Biochemisrty and Cell Biology,* *Chinese Academy of Sciences, China*	

13:55~14:25	**B. Linju Yen, M.D. (顏伶汝副研究員)** **Mechanisms involved in human mesenchymal stem cell (MSC) immunomodulation: interactions with innate and adaptive leukocytes** *Associate Investigator and Attending Physician, Institute of Cellular and Systems Medicine, National Health Research Institutes, Taiwan* **Moderator: Yu-Sun Chang, Ph.D. (張玉生教授)** *Professor, Graduate Institute of Biomedical Sciences, Chang Gung University, Taiwan*	
14:25~14:55	**Ping Hu, Ph.D. (胡蘋研究員)** **Activation of Wnt signaling prevents muscle atrophy** *Professor, Shanghai Institute of Biochemisrty and Cell Biology, Chinese Academy of Sciences, China*	
14:55~15:25	**Yen-Hua Huang, Ph.D. (黃彥華教授)** **Niche regulation of stemness expression in cancer** *Professor and Director, Department of Biochemistry and Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taiwan*	
15:25~15:45	**Coffee Break**	**16F/B1**
	Session VI: Translational Medicine in Cancer **Moderator: Tao-Shih Hsieh, Ph.D. (謝道時院士)** *Academician, Academia Sinica, Taiwan* *Distinguished Research Fellow and Director, Institute of Cellular and Organismic Biology, Academia Sinica, Taiwan*	**16F**
15:45~16:15	**Mien-Chie Hung, Ph.D. (洪明奇院士)** **Novel signaling pathways in cancer cells and development of targeted therapy** *Academician, Academia Sinica, Taiwan* *Professor and Chair, Department of Molecular and Cellular Oncology, MD Anderson Cancer Center, The University of Texas, USA*	
16:15~16:45	**Zhaocai Zhou, Ph.D. (周兆才研究員)** **Development of a peptide-based YAP inhibitor sheds new light on gastric cancer treatment** *Professor, Shanghai Institute of Biochemisrty and Cell Biology, Chinese Academy of Sciences, China*	
	Moderator: Jang-Yang Chang, M.D. (張俊彥院長) *Professor and Dean, College of Medicine, National Cheng-Kung University, Taiwan* *Distinguished Research Fellow, Institute of Cancer Research, National Health Research Institutes, Taiwan*	
16:45~17:15	**Jing-Ping Liou, Ph.D. (劉景平教授)** **Azaindolyl compounds with more selective inhibitory effect on histone deacetylase 6 activity, exhibit antitumor activity in colorectal cancer HCT116 cells** *Professor and Associate Dean, School of Pharmacy, College of Pharmacy, Taipei Medical University, Taiwan*	
17:15~17:45	**Ann-Lii Cheng, M.D., Ph.D. (鄭安理教授)** **Microorganism and cancer: A revisit of the spectrum of *H. Pylori*-related gastric lymphoma** *Professor and Director, Graduate Institute of Oncology, Collage of Medicine, National Taiwan University, Taiwan*	
17:45~18:15	**Award & Closing Remark**	**16F**
08:00~18:00	**Exhibition**	**1F, 16F, B1**

Map Information

Map Guidance



Roads & Streets

A. 220 Lane,WuXing Street
B. Wusing Street(WuXing Street)
C. 284 Lane,WuXing Street
D. 22 Alley,284 Lane,WuXing Street

Entrances

i. University Entrance
ii. Hospital Entrance
iii. Ambulance Entrance

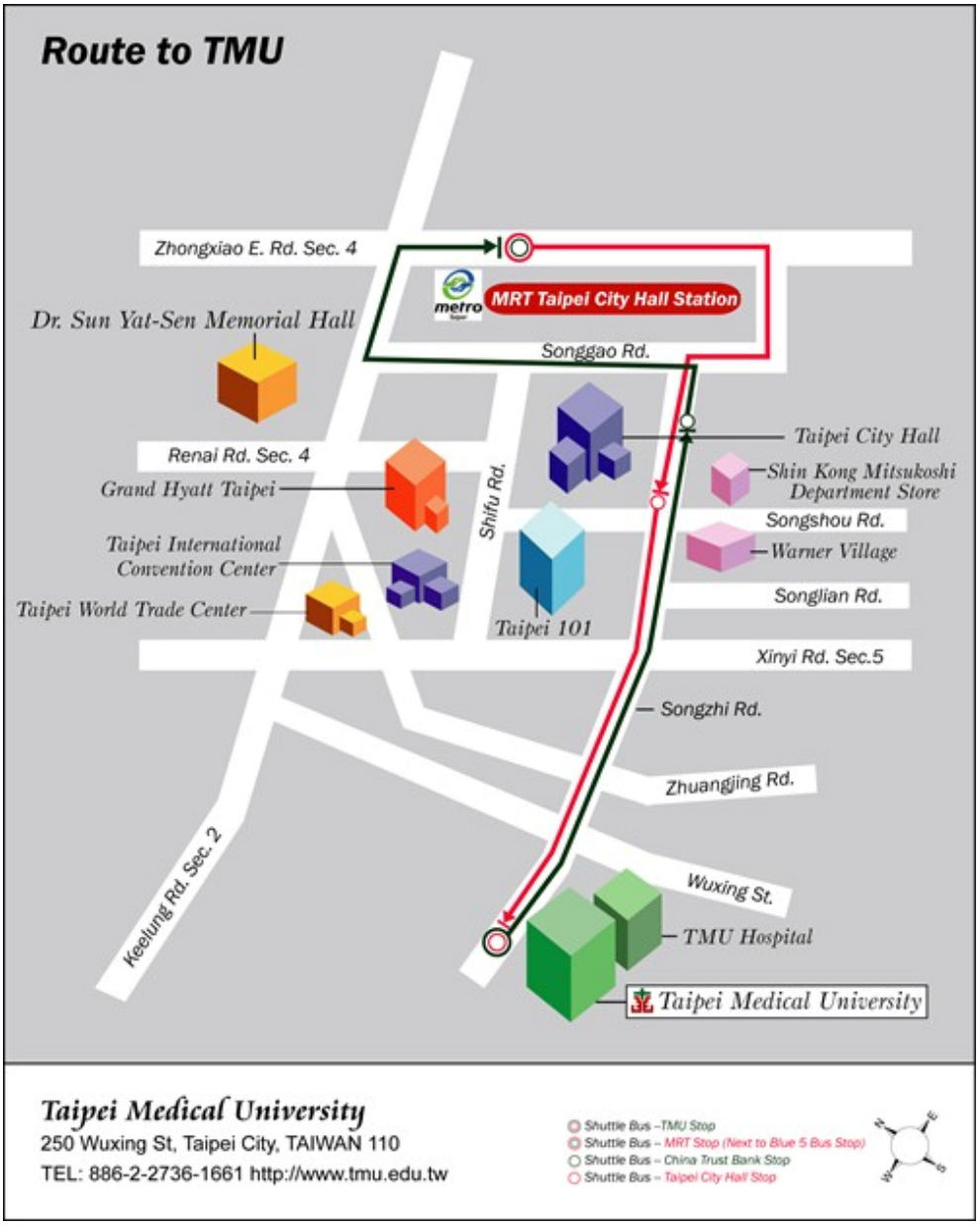
Buildings

1. Health Science Building
2. Auditorium
3. United Medical Building (Front Building)
4. United Medical Building (Back Building)
5. Oral Medicine Building
6. Instruction Building
7. Medical Laboratory Science and Biotechnology Building A
8. Medical Laboratory Science and Biotechnology Building B
9. Morphology Building
10. Gymnasium
11. Mushan Dormitory
12. First Building, Taipei Medical University Hospital
13. Second Building, Taipei Medical University Hospital
14. Third Building, Taipei Medical University Hospital

Transportation

TMU shuttle service

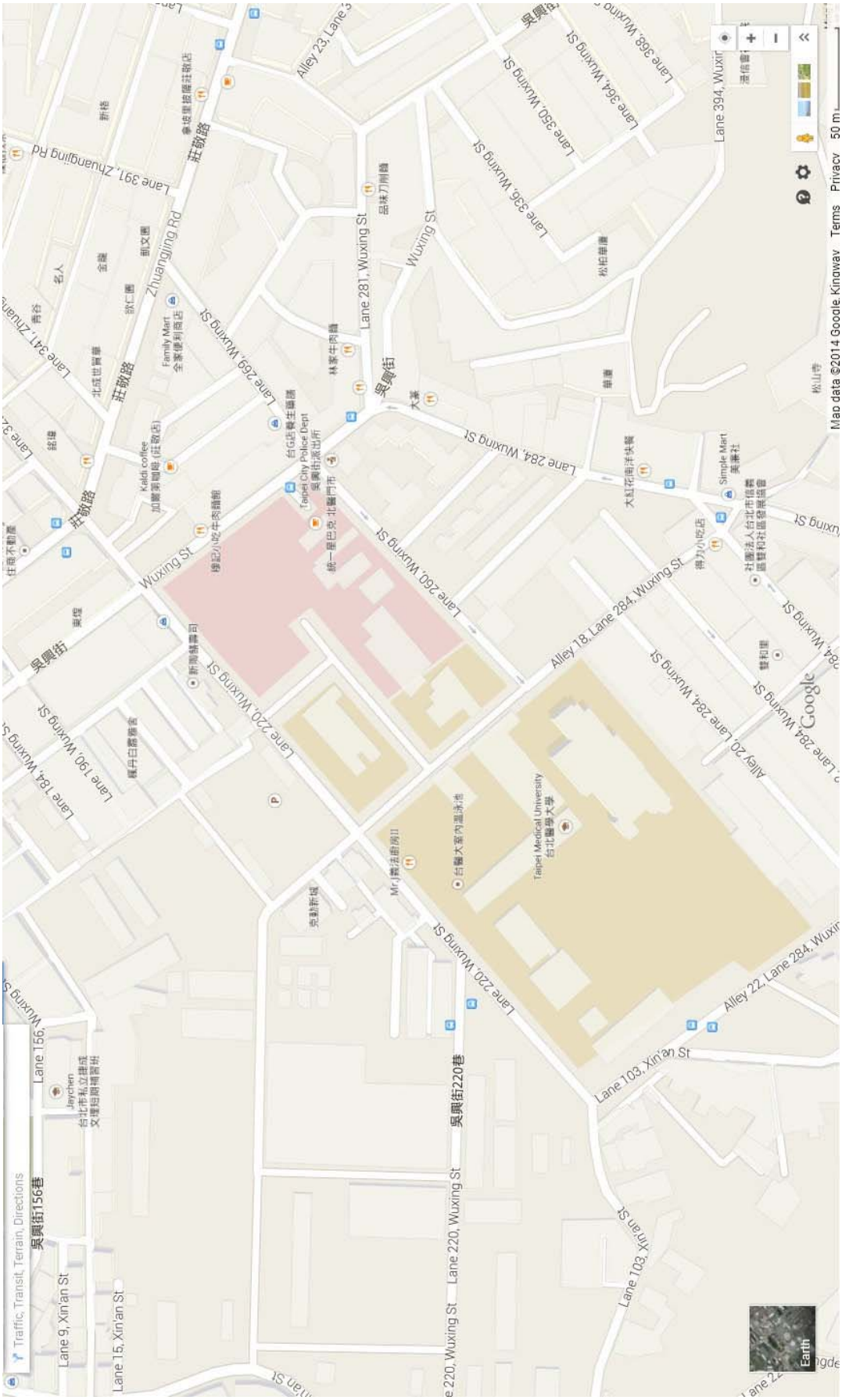
The school is located near MRT Taipei City Hall (Blue Line) and Liuzhangli (Brown Line) stations, and TMU provides shuttle services to both. Buses run every 15 minutes between the City Hall station and TMU (see route map), while the Liuzhangli shuttle bus runs every half an hour.



Public transit

Public transportation to TMU includes bus lines 266, 288, 226, 1, 235, 22, 33 and Blue 5.

Local Map


Lane 281, Wuxing St
Wuxing St
Zhuangjing Rd
莊敬路
吳興街
Lane 259, Wuxing St
Lane 284, Wuxing St
Lane 260, Wuxing St
Alley 18, Lane 284, Wuxing St
Lane 220, Wuxing St
Taipei Medical University
台北醫學大學
Alley 22, Lane 284, Wuxing St
Lane 103, Xin'an St
吳興街220巷
Lane 220, Wuxing St
吳興街156巷
Lane 9, Xin'an St
Lane 15, Xin'an St
Lane 394, Wuxing St
Lane 336, Wuxing St
Lane 350, Wuxing St
Lane 364, Wuxing St
Lane 368, Wuxing St
Alley 23, Lane 3
Lane 391, Zhuangjing Rd
Lane 341, Zhuang
Lane 190, Wuxing St
Lane 184, Wuxing St
Alley 20, Lane 284, Wuxing St
Lane 284, Wuxing St
Traffic, Transit, Terrain, Directions
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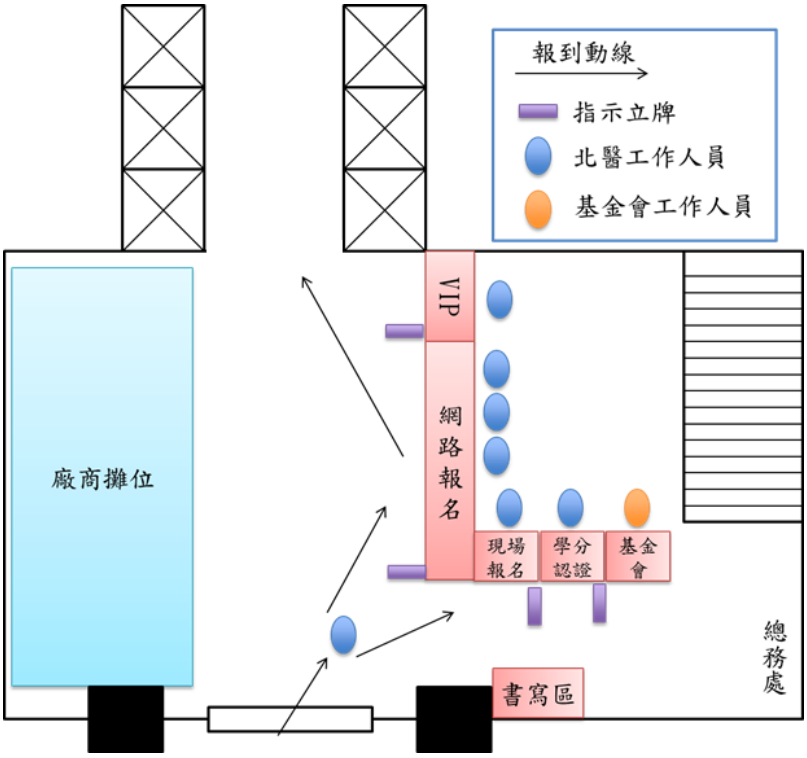
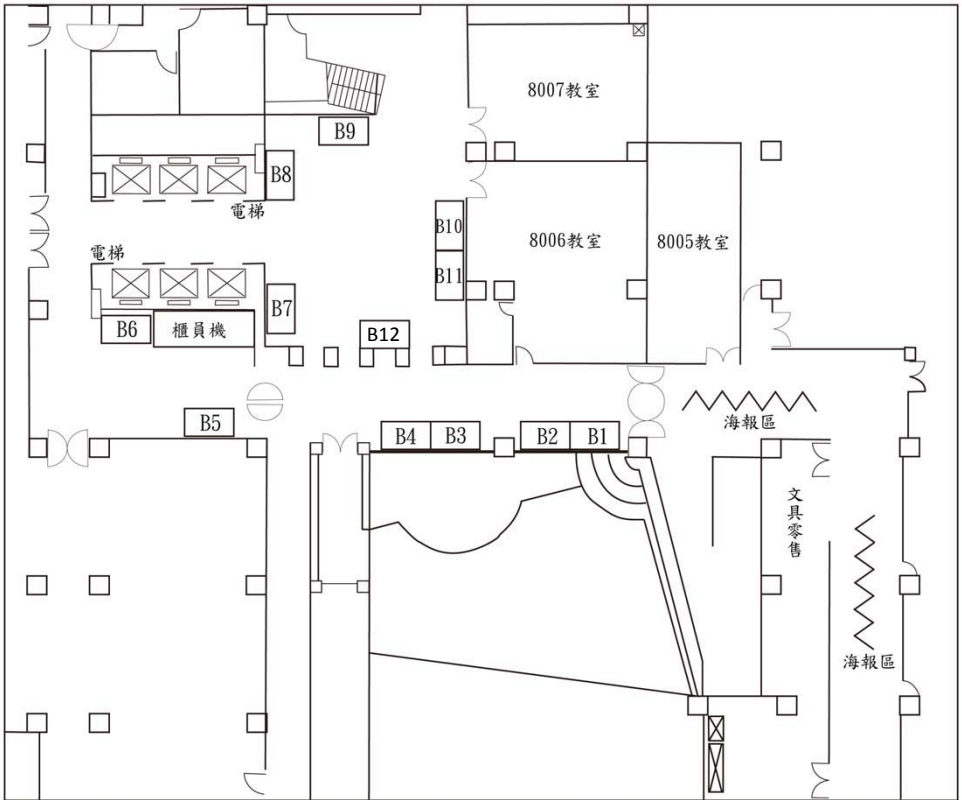
Floor Plan

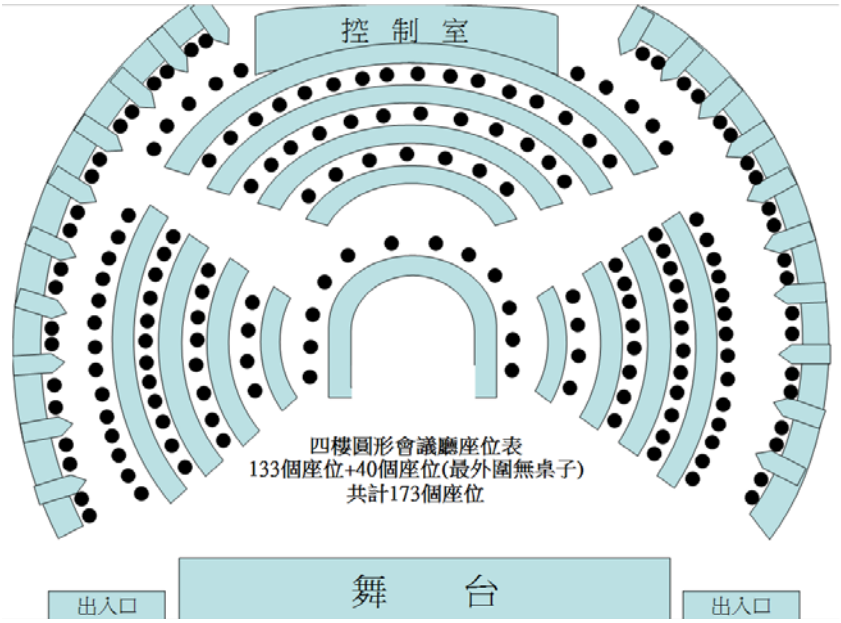
United Medical Back Building, 1 FL.



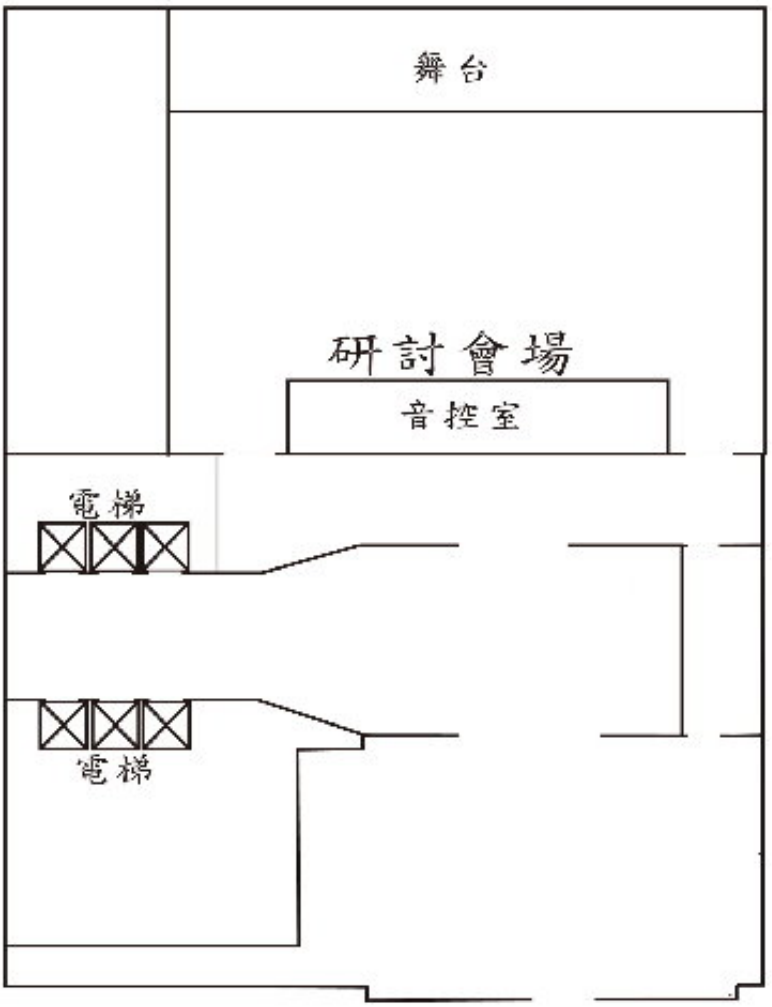
United Medical Back Building, B1 FL.



United Medical Front Building, 4TH FL.



United Medical Back Building, 16F Lecture Hall



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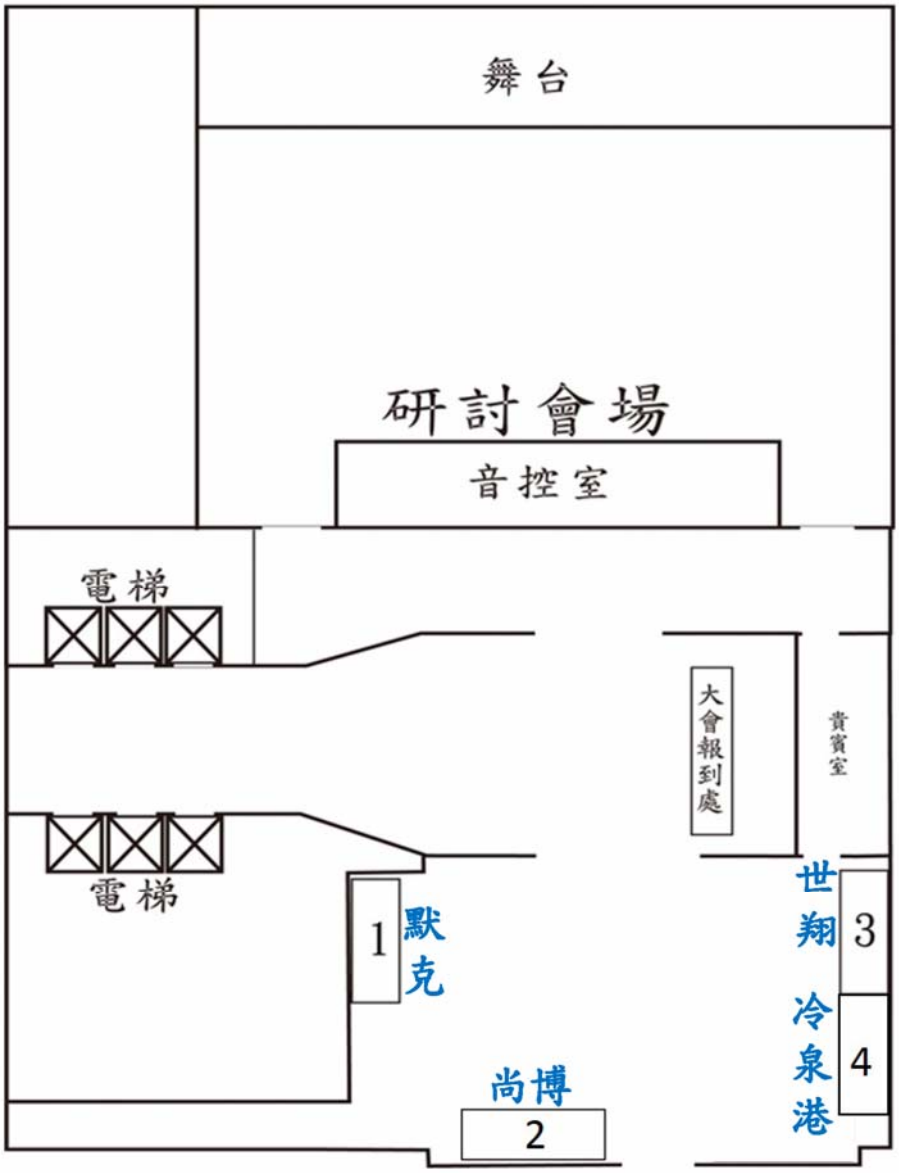
Exhibition Floor Plan

Exhibitor at 16F Hall



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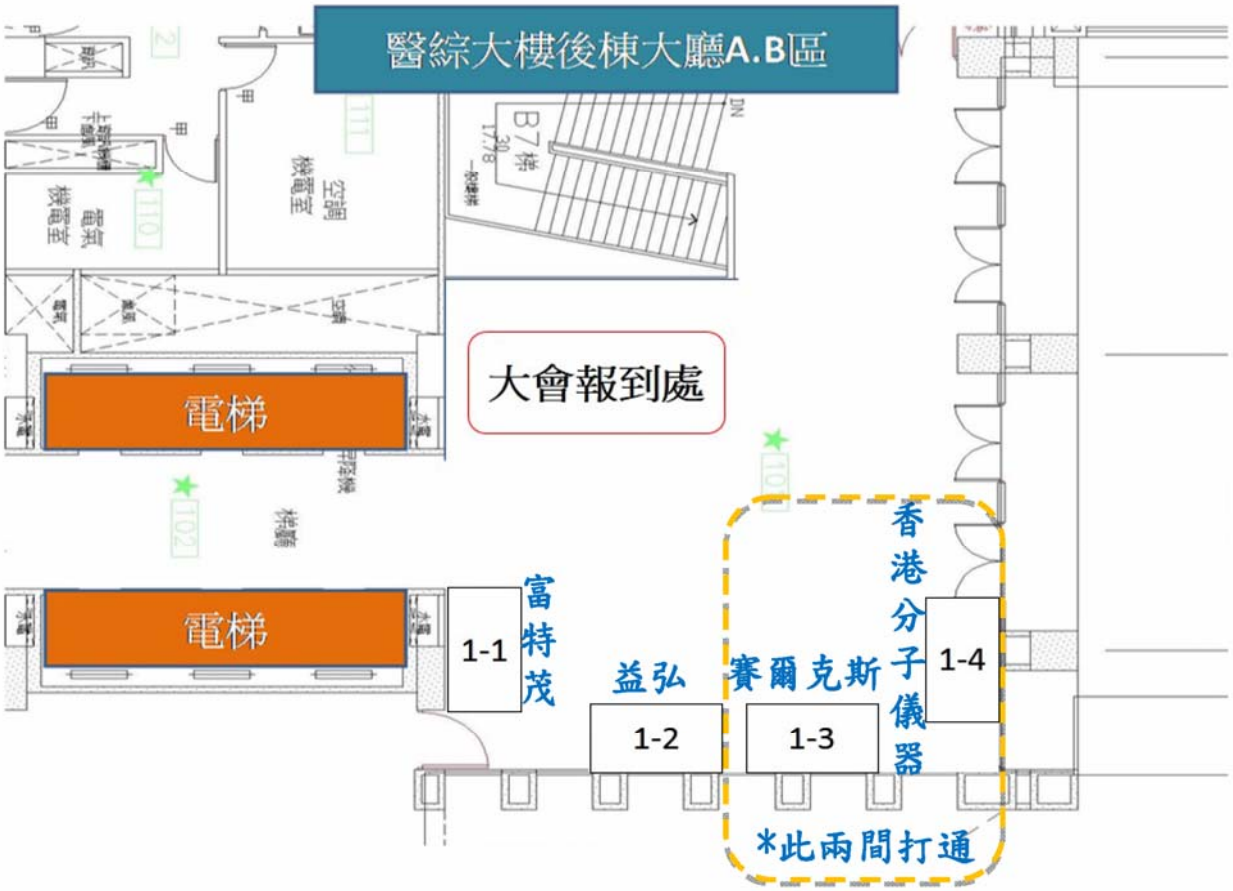
Exhibitor at 1F Lobby



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1F-4: 香港分子儀器有限公司

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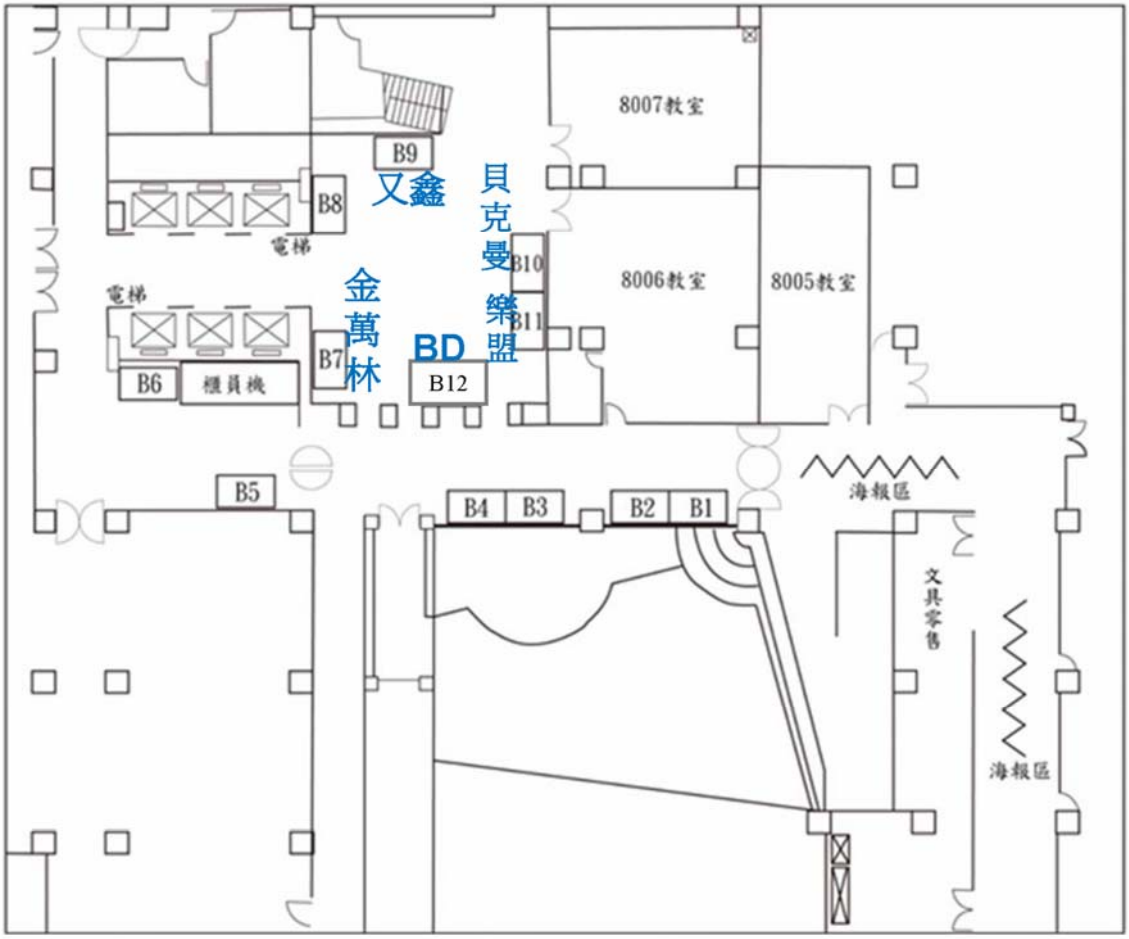

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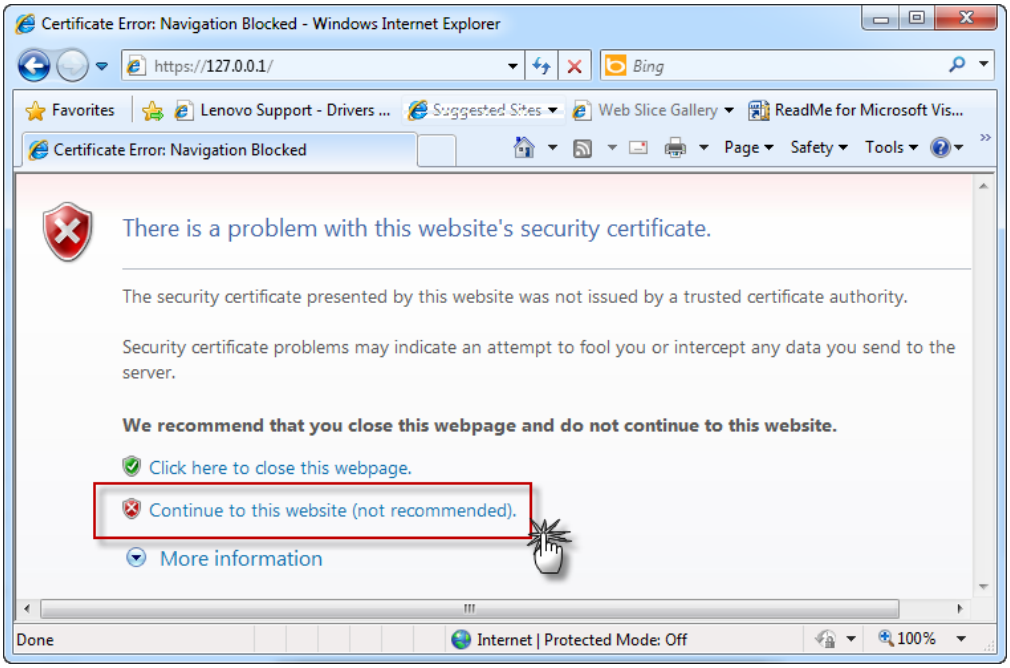

Introduction of Moderator

&

Invited Speaker’s Brief Curriculum Vitae and Abstract

Session I

Chromosome Instability in Cancer Development (I)

Moderator:

Yun Yen, M.D., Ph.D.
(閻雲校長)

Distinguished Professor and President
Taipei Medical University, Taiwan
Dr. & Mrs. Allen Y. Chao Chair
Developmental Cancer Therapeutics,
City of Hope, U.S.A.
Associate Director
Translational Research, City of Hope, U.S.A.
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Molecular Pharmacology, City of Hope, U.S.A.
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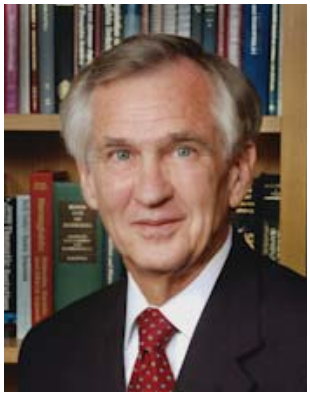
Co-leader
Developmental Cancer Therapeutics,
City of Hope, U.S.A.



Edward J. Benz, Jr. MD.

Academician, American Academy of Arts and Sciences
National Academy of Sciences

President and CEO of Dana Farber Cancer Institute;
Richard and Susan Smith Professor of Medicine,
Genetics and Pediatrics,
Harvard Medical School/Dana-Farber Cancer Institute

Email：edward_benz@dfci.harvard.edu

Recent Selected Publications (Selected from >300 peer-reviewed publications):

◎ Leto TL, Fortugno-Erikson, DM, Harris AS, Barton D, Yang-Feng TL, Francke U, Marchesi VT, **Benz EJ Jr.** (1988) Comparison of non-erythroid α spectrin genes reveals strict homology among diverse species. *Mol Cell Biol* 8:1-9.

◎ **Benz EJ Jr**., Berman BW, Coates T, Tonkonow BL, Boxer LA, Altman A, Adams JG III. (1981) Molecular analysis of the ß-thalassemia phenotype associated with inheritance of hemoglobin E (α2ß226Glu→Lys). *J Clin Invest* 68:118-26.

◎ **Benz EJ Jr.**, Barker JE, Pierce JE, Turner PA, Nienhuis AW. Hemoglobin switching in sheep: Commitment of erythroid stem cells to expression of the ßC globin gene and accumulation of ßC-globin mRNA. (1978) *Cell* 14:733-40.

◎ **Benz EJ Jr.**, Forget BG, Hillman DG, Cohen-Solal M, Pritchard J, Cavallesco C, Housman D. (1978) Variability in the amount of ß globin mRNA in ß0 thalassemia. *Cell* 14:299-312.

◎ **Benz EJ Jr**., Turner PA, Barker J, Nienhuis AW. (1977) Stability of the individual globin genes during erythroid differentiation. *Science* 196:1213-14.

◎ Nienhuis AW, Turner P, **Benz EJ Jr.** Relative stability of α- and ß-globin messenger RNAs in homozygous ß+ thalassemia. (1977) *Proc Natl Acad Sci* 74:3960-4.

◎ Nienhuis AW, **Benz EJ Jr**. Regulation of hemoglobin synthesis during the development of the red cell. (1977) A Medical Progress Article for the *New England Journal of Medicine* 297:1318-28, 1371-81, 1430-6.

◎ **Benz EJ Jr.**, Nathan DG (1975) Thalassemia: Applying molecular genetics to a human disease. *Nature* 256:163-4.

◎ Forget BG, **Benz EJ Jr.**, Skoultchi A, Baglioni C, Housman D. (1974) Absence of messenger RNA for ß globin in ß0 thalassemia. *Nature* 247:379-81.

◎ Housman D, Forget BG, Skoultchi A, **Benz EJ Jr.** (1973) Quantitative deficiency of chain-specific globin messenger ribonucleic acids in the thalassemia syndromes. *Proc Natl Acad Sci (USA)* 70:1809-13.

Toward high precision cancer medicine: lessons learned

Edward J. Benz
Dana Farber Cancer Institute/
Harvard Medical School, USA

The combined effects of the sequencing of the human genome, the early success of targeted therapy with a signal transduction inhibitor (imatinib) for chronic myelogenous leukemia (CML), and the recognition that some targeted therapies were effective in diverse forms of cancer sharing similar molecular profiles have given rise to the hope that the treatment of individual cancer patients could be customized to attack the unique biological misbehaviors of his or her tumor. This approach has been variously termed “personalized cancer medicine”, “individualized cancer medicine” or “high precision cancer medicine”. The latter designation will be used in this presentation. In contrast to the first two terms, it does not pre-suppose that a unique therapy will be available for every patient, at least initially, nor does the term contaminate the broader interpersonal and psycho-social dimensions inherent in efforts to make care truly individualized and personalized. The earliest efforts to utilize molecular profiling of tumors to guide more precise therapies for individual patients have met with remarkable success in a few cases. Unfortunately, the paradigm has proven to be extraordinarily difficult to apply widely to most patients. There appear to be many reasons for this limited success. The tumors in many patients do not have obvious “driver” mutation against which a targeted agent is available; resistance against the (usually) single targeted agent can develop rapidly, etc. This presentation will review progress toward the achievement of high precision cancer treatments on a wide scale and on reflect one major cancer center’s efforts to generate the necessary diagnostic information for precision therapy on an enterprise scale.

JoAnne Stubbe, Ph.D.

Academician, American Academy of Arts and Sciences
National Academy of Sciences

Novartis Professor of Chemistry and Biology,
Massachusetts Institute of Technology (MIT)

Email：stubbe@mit.edu

Recent Selected Publications (Selected from >300 peer-reviewed publications):

◎ **Stubbe J** and Ackles D (1980) On the Mechanism of Ribonucleoside Diphosphate Reductase from *E. coli*: Evidence for 3'-C-H Bond Cleavage. *J. Biol. Chem*., 255, 8027.

◎ Ator M and **Stubbe J** (1985) Mechanism of Inactivation of *Escherichia coli* Ribonucleotide Reductase by 2'-Chloro-2'-deoxyuridine 5'-Diphosphate: Evidence for Generation of a 2'-Deoxy-3'-ketonucleotide via a Net l,2 Hydrogen Shift. *Biochemistry*, 24, 7214.

◎ Kozarich JW, Worth Jr. L, Frank BL, Christner DF, Vanderwell DE and **Stubbe J**, (1989) Sequence-Specific Isotope Effects on the Cleavage of DNA by Bleomycin. *Science*, 245, 1396.

◎ Bollinger JM, Edmondson DE, Huynh BH, Filley J, Norton J and **Stubbe J** (1991) Mechanism of Assembly of the Tyrosyl Radical-Dinuclear Iron Cluster Cofactor of Ribonucleotide Reductase. *Science*, 253, 292.

◎ Mueller EJ, Meyer E, Rudolph J, Davisson VJ and **Stubbe J** (1994) N^5-Carboxyaminoimidazole Ribonucleotide: Evidence for a New Intermediate and Two New Enzymatic Activities in the *de novo* Purine Biosynthetic Pathway of *Escherichia Coli*. *Biochemistry*, 33, 2269-2278.

◎ Licht S, Gerfen GJ and **Stubbe J** (1996) Thiyl Radicals in Ribonucleotide Reductases. *Science*, 271, 477-481.

◎ Wu W, Vanderwall DE, Turner CJ, Kozarich JW and **Stubbe J** (1996) Solution Structure of Co•Bleomycin A2 Green Complexed with DNA Oligonucleotide d(CCAGGCCTGG). *J. Am. Chem. Soc*., 118, 1281-1294.

◎ Burdi D, Willems J-P, Riggs-Gelasco P., Antholine WE, **Stubbe J**, and Hoffman BM (1998) The Core Structure of X Generated in the Assembly of the Diiron Cluster of Ribonucleotide Reductase: $^{17}O_2$ and $H_2\,^{17}O$ ENDOR. *J. Am. Chem. Soc.* 120, 12910-12919.

◎ Lawrence CC, Bennati M, Obias HV, Bar G, Griffin RG and **Stubbe J** (1999) High-Field EPR Detection of a Disulfide Radical Anion in the Reduction of Cytidine 5'-diphosphate by the E441Q R1 Mutant of *Escherichia coli* Ribonucleotide Reductase. *Proc. Natl. Acad. Sci.* USA, 96, 8979-8984.

◎ Change MCY, Yee CS, **Stubbe J** and Nocera DG (2004) Turning on Ribonucleotide Reductase by Light-Initiated Amino Acid Radical Generation. *Proc. Natl. Acad. Sci.* USA. 101(18):6882-7.

◎ Seyedsayamodost MR, **Stubbe J** and Bennati M (2007) Peldor Spectrsocopy with DOPA- and NH_2Y-α2: Distance Measurements between residues involved in the Radical propagation pathway of *E. coli* Ribonucleotide Reductase. *J. Am Chem. Soc* 129, 15748-9.

◎ Seyedsayamdost MR, Xie J, Chan CT, Schultz PG and **Stubbe J** (2007) Site specific insertion of 3-aminotyrosine into the α2 subunit of *E. coli* Ribonucleotide Reductase: Direct Evidence for the Role of Y730 and Y731 in Radical propagation. *J. Am. Chem. Soc*. 129, 15060-71.

◎ Boak AK., Cotruvo JA Jr, **Stubbe, J.** and Rosenzweigh, AC (2010) Structural Basis for Activation of Class Ib Ribonucleotide Reductase. Science 329, 1526-30.

◎ Yokoyama K, Smith AA, Corzilius B, Griffin RG and **Stubbe J** (2011) Equilibration of tyrosyl radicals (Y356•, Y731•, Y730•) in the radical propagation pathway of the *E. coli* class Ia ribonucleotide reductase. *J. Am. Chem. Soc* 143, 18420-432.

◎ Aye Y, Brignole EJ, Long MJ, Chittuluru J, Drennan CL, Asturias FJ and **Stubbe J** (2012) Clofarabine 5'-di and –triphosphates inhibit human ribonucleotide reductase by altering the quaternary structure of its large subunit. Chem Biol 19 799-805.

Radicals your life is in their hands: ribonucleotide reductases as a paradigm

JoAnne Stubbe
Massachusetts Institute of Technology, USA

It will come as a surprise to many chemists and biologists, that Nature uses free radical chemistry in essential metabolic pathways. She has figured out how to harness the considerable reactivity of these species to carry out very difficult chemical transformations with exquisite specificity. I will discuss the role of “good” radicals in biology using ribonucleotide reductases (RNRs) as a paradigm, a problem that my lab has investigated for 30 years. Specifically we will give an overview of these complex enzymes: the complex, radical-mediated reduction chemistry, the radical initiation process that occurs over 35 angstroms, the biosynthetic pathways required for the essential dimetal-tyrosyl radical cofactor biosynthesis and maintenance, and the importance of deoxynucleotides and ATP in the regulation of quaternary structure which governs RNR activity. Each of these topics as a target for new anticancer therapeutics will be discussed.

Session I

Chromosome Instability in Cancer Development (I)

Moderator:

Wen-Chang Chang, Ph.D.
(張文昌院士)

Academician
Academia Sinica, Taiwan

Distinguished Professor
Graduate Institute of Medical Sciences,
Taipei Medical University, Taiwan

Director of the board
Taipei Medical University, Taiwan

Wen-Hwa Lee, Ph.D. (李文華院士)

Academician, Academia Sinica, Taiwan

Professor and President, China Medical University, Taiwan
Donald Bren Professor of Biomedicine,
Department of Biological Chemistry, University of California,
Irvine, U.S.A.
Email：whlee@mail.cmu.edu.tw

Recent Selected Publications

◎ Chang YC, Yu YH, Shew JY, Lee WJ, Hwang JJ, Chen YH, Chen YR, Wei PC, Chuang LM and **Lee WH** (2013) Deficiency of NPGPx, an oxidative stress sensor, leads to obesity in mice and human. *EMBO Molecular Medicine* 5(8) 1165-1179.

◎ Huang CK, Yang CY, Jeng YM, Chen CL, Wu HH, Chang YC, Ma C, Kuo WH, Chang KJ, Shew JY and **Lee WH**. (2013) Autocrine/paracrine mechanism of interleukin-17B receptor promotes breast tumorigenesis through NF-κB-mediated antiapoptotic pathway. *Oncogene.* Jul 15. [Epub ahead of print]

◎ Wei PC, Wang ZF, Lo WT, Su MI, Shew JY, Chang TC and **Lee WH** (2013) A cis-element with mixed G-quadruplex structure of NPGPx promoter is essential for nucleolin-mediated transactivation on non-targeting siRNA stress. *Nucleic acids research* 41(3) 1533-1543.

◎ Zhu J, Zhou L, Wu G, Konig H, Lin X, Li G, Qiu XL, Chen CF, Hu CM, Goldblatt E, Bhatia R, Chamberlin AR, Chen PL and **Lee WH** (2013) A novel small molecule RAD51 inactivator overcomes imatinib-resistance in chronic myeloid leukaemia. *EMBO molecular medicine* 5(3) 353-365.

◎ Ngo B, Hu CM, Guo XE, Ngo B, Wei R, Zhu J and **Lee WH** (2013) Complementary Interhelical Interactions between Three Buried Glu-Lys Pairs within Three Heptad Repeats Are Essential for Hec1-Nuf2 Heterodimerization and Mitotic Progression. *The Journal of biological chemistry* 288(48) 34403-34413.

◎ Hwang-Verslues WW, Chang PH, Jeng YM, Kuo WH, Chiang PH, Chang YC, Hsieh TH, Su FY, Lin LC, Abbondante S, Yang CY, Hsu HM, J Yu JC, Chang KJ, Shew JY, Lee EYPH and **Lee WH** (2013) Loss of corepressor PER2 under hypoxia upregulates OCT1-mediated EMT gene expression and enhances tumor malignancy. *Proceedings of the national academy of sciences of the United States of America* 110(30) 12331-12336.

◎ He S, Ni D, Ma B, Lee JH, Zhang T, Ghozalli I, Pirooz SD, Zhao Z, Bharatham N, Li B, Oh S, **Lee WH**, Takahashi Y, Wang HG, Minassian A, Feng P, Deretic V, Pepperkok R, Tagaya M, Yoon HS, Liang C (2013) PtdIns(3)P-bound UVRAG coordinates Golgi-ER retrograde and Atg9 transport by differential interactions with the ER tether and the beclin 1 complex. *Nature cell biology* 15(10) 1206-1219.

◎ Chang PH, Hwang-Verslues WW, Chang YC, Chen CC, Hsiao M, Jeng YM, Chang KJ, Lee EY, Shew JY* and **Lee WH*** (2012) Activation of Robo1 signaling of breast cancer cells by Slit2 from stromal fibroblast restrains tumorigenesis via blocking PI3K/Akt/beta-catenin pathway. *Cancer research*72(18) 4652-4661.

◎ Wei PC, Hsieh YH, Su MI, Jiang X, Hsu PH, Lo WT, Weng JY, Jeng YM, Wang JM, Chen PL, Chang YC, Lee KF, Tsai MD, Shew JY* and **Lee WH*** (2012) Loss of the Oxidative Stress Sensor NPGPx Compromises GRP78 Chaperone Activity and Induces Systemic Disease. *Molecular cell* 48(5) 747-759.

◎ Chen PL, Chen CF, Chen Y, Guo XE, Huang CK, Shew JY, Reddick RL, Wallace DC and **Lee WH** (2012) Mitochondrial genome instability resulting from SUV3 haploinsufficiency leads to tumorigenesis and shortened lifespan. *Oncogene* 32(9) 1193-1201.

Targeting tumor suppressor networks for therapeutic application

Wen-Hwa Lee
China Medical University, Taiwan

An attractive approach to developing new anticancer drugs is to target genes or proteins that are essential for tumor cell growth and survival. Tumor suppressors play an essential role in the development of cancer. During the past decades, elucidation of fundamental function of tumor suppressors and its networks allows us to further explore its potentials for therapeutic application. The prototypic tumor suppressor, RB, a key cell cycle regulator, will serve as an example for this purpose. In addition, RB interacting protein, Hec1, which is a mitotic regulator, and a BRCA interacting protein, Rad51, which is a DNA recombinase, emerge as interesting targets. We have identified and generated derivatives of small compound inhibitors targeting these pathways and demonstrated the efficacy of these compounds. Furthermore, we have identified that IL17RB pathway plays an essential role in pancreatic cancer metastasis and generated neutralizing antibodies against IL17RB for blocking pancreatic cancer metastasis. This illustrates the differential approach based on the targets toward therapeutic application for cancer treatment.

Ying Huang, Ph.D. (黃昊研究員)

Professor
Shanghai Institute of Biochemistry and Cell Biology,
Chinese Academy of Sciences

Email: huangy@sibcb.ac.cn

Recent Selected Publications

◎ Zhu F, Erlandsen H, Ding L, Li J, **Huang Y**, Zhou M, Liang X, Ma J and Wu H. (2011) Structural and Functional Analysis of a New Subfamily of Glycosyltransferases Required for Glycosylation of Serine-rich Streptococcal Adhesins. *J Biol Chem*. 286:27048-57.

◎ Liu H*, Wang JYS*, **Huang Y***, Li Z, Gong W, Lehmann R and Xu RM. (2010) Structure basis for methylarginine-dependent recognition of Aubergine by Tudor. *Genes & Development*. 24:1876-1881. (* co-first author)

◎ **Huang Y**, Ji L, Huang Q, Vassylyev DG, Chen X and Ma JB. (2009) Structural insights into mechanisms of the small RNA methyltransferase HEN1. *Nature*. 461: 823-827.

◎ **Huang Y**, Fang J, Bedford MT, Zhang Y and Xu RM. (2006) Recognition of histone H3 lysine-4 methylation by the double tudor domain of JMJD2A. *Science*. 312: 748-751.

◎ **Huang Y**, Myers MP and Xu RM. (2006) Crystal structure of the HP1-EMSY complex reveals an unusual mode of HP1 binding. *Structure*. 14: 703-712. (cover story)

◎ **Huang Y**, Huang Q, Chen H, Tang Y, Miyake H and Kusunoki M. (2003) Crystallization and preliminary crystallographic study of rBmKalphaIT1, a recombinant alpha-insect toxin from the scorpion Buthus martensii Karsch. *Acta Crystallogr D Biol Crystallogr*. D59:1635-1636.

Structural studies of Rhino protein in piRNA biogenesis

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Small-RNA-guided gene regulation is a common biological process in eukaryotic cells. Animal germ cells are characterized by an intriguing small-RNA-mediated gene-silencing mechanism known as PIWI pathway. PIWI-interacting RNAs (piRNAs) are small, 21-30 nt single-stranded RNAs that associate with PIWI proteins. The function of piRNA is silencing transposon elements in germ line cells to keep the genome integrity since germ line cells are the only source for transmitting genetic information to the next generation. For a long time the biogenesis of piRNA and the mechanism of how it functions remains unclear. The biogenesis of piRNAs is quite different from that of other small-RNA pathways, which is independent of Dicer. piRNA biogenesis occurs through both primary and secondary pathway (or called ping-pong cycle). In drosophila transcripts from heterochromatic clusters are processed into primary piRNAs. A particularly fast evolving homologue of heterochromatin protein 1 (HP1) called Rhino binds to dual-strand piRNA clusters and is required for their production. But how does Rhino recognize histone H3 trimethylated on lysine 9? What's the difference between Rhino and other HP1 proteins? Here we show the crystal structure of Rhino both in apo form and complex form with H3K9me3. We observed a unique dimer interface in Rhino and a domain-swapping in conformational change. These findings provide insights into the molecular mechanism of the specificity of Rhino recognizing histone H3K9me3 and its function in piRNA biogenesis.

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Recent Selected Publications

◎ Zong FY, Fu X, Wei WJ, Luo YG, Heiner M, Cao LJ, Fang Z, Fang R, Lu D, Ji H, **Hui J**. (2014) The RNA-binding protein QKI suppresses cancer-associated aberrant splicing. *PLOS Genet*, 10, e1004289

◎ Wei WJ*, Mu SR*, Heiner M, Fu X, Cao LJ, Gong XF, Bindereif A, **Hui J**. (2012) YB-1 binds to CAUC motifs and stimulates exon inclusion by enhancing the recruitment of U2AF to weak polypyrimidine tracts. *Nucleic Acids Res*, 40, 8622-8636

◎ Huang Y, Li WC, Yao X, Lin QJ, Yin JW, Liang Y, Heiner M, Tian B, **Hui J**, Wang G. (2012) Mediator complex regulates alternative mRNA processing via the Med23 subunit. *Mol Cell*, 45, 459-469

◎ Hung LH*, Heiner M*, **Hui J***, Schreiner S, Benes V, Bindereif A. (2008) Diverse roles of hnRNP L in mammalian mRNA processing: a combined microarray and RNAi analysis. *RNA*, 14, 284-296

◎ **Hui J***, Hung LH*, Heiner M, Schreiner S, Neumuller N, Reither G, Haas SA, Bindereif A. (2005) Intronic CA-repeat and CA-rich elements: a new class of regulators of mammalian alternative splicing. *EMBO J*, 24, 1988-1998

◎ **Hui J**, Reither G, Bindereif A. (2003) Novel function role of CA repeats and hnRNP L in RNA stability. *RNA*, 9, 931-936

◎ **Hui J**, Stangl K, Lane WL, Bindereif A. (2003) HnRNP L stimulates splicing of the eNOS gene by binding to variable-length CA repeats. *Nat Struct Biol*, 10, 33-37

The RNA-binding protein QKI suppresses lung cancer-associated aberrant splicing

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Lung cancer is the leading cause of cancer-related death worldwide. Aberrant splicing has been implicated in lung tumorigenesis. However, the functional links between splicing regulation and lung cancer are not well studied. To understand the role of RNA-binding proteins in lung tumorigenesis, we analyzed the public database and observed that RNA-binding protein QKI is down-regulated in non-small cell lung cancer (NSCLC) tissues and that its down-regulation is significantly associated with a poorer prognosis. Using a combined RNAi and RNA-Seq analysis, we identified several hundreds of alternatively spliced genes regulated by QKI and validated at least 24 lung cancer-related events in lung cancer tissues. We have obtained evidence that QKI inhibits cell proliferation through isoform-switch of its targets. To understand the mechanism of splicing regulation by QKI, we generated an RNA map of QKI and revealed that QKI can positively and negatively control exon inclusion in a binding-site position-dependent manner. We further showed that QKI inhibits splicing by selectively competing with a core splicing factor, SF1. Our findings demonstrate that QKI is a critical splicing regulator in lung cancer cells and contributes to lung tumorigenesis by modulating alternative splicing of its targets.

Session II

Cancer Metabolism and Signaling

Moderator:

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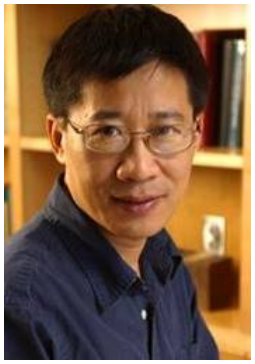

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Recent Selected Publications

◎ Yan J, Xiang J, Lin Y, Ma J, Zhang J, Zhang H, Sun J, Danial N, Liu J, **Lin A***. (2013) Inactivation of the BH3-only Protein BAD by IKK Inhibits TNFα-induced Apoptosis Independently of NF-κB Activation. *Cell* 152: 304-315.

◎ Liu J, Yan J, Jiang S, Wen J, Cheng L, Zhao Y, and **Lin A***. (2012) Site-specific ubiquitination is required for relieving Miz1-mediated suppression on TNFα-induced JNK activation and inflammation. *Proceedings of the National Academy of Science USA* 109:191-6.

◎ Liu J, Zhao Y, Eilers M, and **Lin A***. (2009) Miz1 is a signal- and pathway-specific modulator or regulator (SMOR) that suppresses TNF-a-induced JNK1 activation. *Proceedings of the National Academy of Science USA*. 106(43):18279-84.

◎ Liu J, Yang D, Minemoto Y, Leitges M, Rosner M.R and **Lin A***. (2006) NF-kB via PKCd promotes JNK activation by UV. *Molecular Cell*. 21:467-480.

◎ Yu C, Minemoto Y, Zhang J, Liu J, Tang F, Bui T, Xiang J*, and **Lin A***. (2004) JNK suppresses apoptosis via phosphorylation of the proapoptotic Bcl-2 family protein BAD. *Molecular Cell.* 13:329-40.

◎ Tang G, Minemoto Y, Dibling B, Purcell NH, Li Z, Karin M, and **Lin A***. (2003) Inhibition of JNK activation by NF-kB target genes. *Nature*. 414:313-317, 2001. - News and Views, Nature. 414:265-266, 2001; Highlights, Nature Reviews, 2: 875, 2001; Hot Papers, The Scientist, 12:32-33.

◎ Tang G, Yang J, Minemoto Y, and **Lin A***. (2001) Blocking caspase-3-mediated proteolysis of IKKb suppresses TNF-a-induced apoptosis. *Molecular Cell.* 8:1005-1016.

◎ Purcell NH, Tang G, Yu C, Mercurio F, DiDonato JA, and **Lin A***. (2001) Activation of NF-kB is required for hypertrophic growth of primary rat neonatal ventricular cardiomyocytes. *Proceedings of the National Academy of Science USA*. 98:6668-6673.

◎ **Lin A**, Minden A, Martinetto H, Claret FX, Lange-Carter C, Mercurio F, Johnson GL, and Karin M. (1995)Identification of a dual specificity kinase that activates the Jun kinases and p38-Mpk2. *Science*. 268:286-290.

◎ **Lin A**, Frost J, Deng T, Smeal T, Al-Alawi N, Kikkawa U, Hunter T, Brenner A, and Karin M. (1992) Casein kinase II is a negative regulator of c-Jun DNA binding and AP-1 activity. *Cell*. 70:777-789.

Computational modeling of IKK signaling

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IKK is essential for inhibition of TNFα-induced apoptosis. The survival role of IKK is thought to be mediated by activation of NF-κB, which induces anti-apoptotic proteins (IAPs) and also prevents prolonged JNK1 activation. Recently, we found that phosphorylation and inactivation of pro-death Bcl-2 family protein BAD by IKK is required for cell survival upon TNFα stimulation, suggesting that activation of NF-κB by IKK is necessary but not sufficient to suppress cell death. We will discuss the mathematic model that reveals the underlying mechanism by which IKK suppresses TNFα-induced apoptosis in the meeting.

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Recent Selected Publications

◎ Chang PC, Wang TY, Chang YT, Chu CY, Lee CL, Hsu HW, Zhou TA, Wu Z, Kim RH, Desai SJ, Liu S, **Kung HJ**. (2014) Autophagy pathway is required for IL-6 induced neuroendocrine differentiation and chemoresistance of prostate cancer LNCaP cells. *PLoS One.* 9(2):e88556.

◎ Chang PC, Cheng CY, Campbell M, Yang YC, Hsu HW, Chang TY, Chu CH, Lee YW, Hung CL, Lai SM, Tepper CG, Hsieh WP, Wang HW,Tang CY, Wang WC, **Kung HJ**. (2013) The chromatin modification by SUMO-2/3 but not SUMO-1 prevents the epigenetic activation of key immune-related genes during Kaposi's sarcoma associated herpesvirus reactivation. BMC Genomics. 23;14:824.

◎ Izumiya Y, Kobayashi K, Kim KY, Pochampalli M, Izumiya C, Shevchenko B, Wang DH, Huerta SB, Martinez A, Campbell M, **Kung HJ**. (2013) Kaposi's sarcoma-associated herpesvirus K-Rta exhibits SUMO-targeting ubiquitin ligase (STUbL) like activity and is essential for viral reactivation. *PLoS Pathog.* 9(8):e1003506.

◎ Guo W, Liu R, Bhardwaj G, Ma AH, Changou C, Yang JC, Li Y, Feng C, Luo Y, Mazloom A, Sanchez E, Wang Y, Huang W, Patterson R,Evans CP, Lam KS, **Kung HJ**. (2013) CTA095, a novel Etk and Src dual inhibitor, induces apoptosis in prostate cancer cells and overcomes resistance to Src inhibitors. PLoS One. 15;8(8):e70910.

◎ Guo W, Liu R, Ono Y, Ma AH, Martinez A, Sanchez E, Wang Y, Huang W, Mazloom A, Li J, Ning J, Maverakis E, Lam KS, **Kung HJ**. (2012) Molecular characteristics of CTA056, a novel interleukin-2-inducible T-cell kinase inhibitor that selectively targets malignant T cells and modulates oncomirs. *Mol Pharmacol.* 82(5):938-47.

◎ **Kung HJ**. (2011) Targeting tyrosine kinases and autophagy in prostate cancer. *Horm Cancer.* 2(1):38-46.

◎ Chang PC, Fitzgerald LD, Hsia DA, Izumiya Y, Wu CY, Hsieh WP, Lin SF, Campbell M, Lam KS, Luciw PA, Tepper CG, **Kung HJ**. (2011) Histone demethylase JMJD2A regulates Kaposi's sarcoma-associated herpesvirus replication and is targeted by a viral transcriptional factor. *J Virol.* 85(7):3283-93.

◎ Wu Z, Chang PC, Yang JC, Chu CY, Wang LY, Chen NT, Ma AH, Desai SJ, Lo SH, Evans CP, Lam KS, **Kung HJ**. (2010) Autophagy Blockade Sensitizes Prostate Cancer Cells towards Src Family Kinase Inhibitors. *Genes Cancer.* 1(1):40-9.

◎ Chang PC, Izumiya Y, Wu CY, Fitzgerald LD, Campbell M, Ellison TJ, Lam KS, Luciw PA, **Kung HJ**. (2010) Kaposi's sarcoma-associated herpesvirus (KSHV) encodes a SUMO E3 ligase that is SIM-dependent and SUMO-2/3-specific. *J Biol Chem.* 285(8):5266-73.

◎ Chang PC, Fitzgerald LD, Van Geelen A, Izumiya Y, Ellison TJ, Wang DH, Ann DK, Luciw PA, **Kung HJ**. (2009) Kruppel-associated box domain-associated protein-1 as a latency regulator for Kaposi's sarcoma-associated herpesvirus and its modulation by the viral protein kinase. *Cancer Res.* 69(14):5681-9. doi: 1

◎ Ellison TJ, Izumiya Y, Izumiya C, Luciw PA, **Kung HJ**. (2009) A comprehensive analysis of recruitment and transactivation potential of K-Rta and K-bZIP during reactivation of Kaposi's sarcoma-associated herpesvirus. *Virology.* 387(1):76-88.

Metabolism and cancer therapeutics: targeting arginine addiction of cancers

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There is considerable evidence that tumor and normal cells differ in their metabolic requirements. The most prominent examples are the addiction of tumor cells to glucose (i.e., Warburg effect) and to glutamine. Therapeutics based on selective targeting of these metabolic pathways is under intensive investigations. Recently, we reported that irrespective of androgen receptor status, prostate cancer cells selectively and epigenetically suppress the expression of ASS (arginine succinosythethase), a rate-limiting enzyme for intracellular arginine synthesis. Analysis of over 100 PC specimens showed the complete absence of ASS expression, whereas some normal prostate epitheial cells express ASS. As a result, PC cells, but not normal counterparts become "auxotroph" for and addicted to external arginine. Thus, arginine-deprivation should selectively "starve" the PC cells to death. Indeed, in recent publications, we showed that depletion of external arginine by arginine deiminase (ADI) effectively induces cell death of CRPC cell lines, but not normal prostate epithelial cells *in vitro* and *in vivo*. In addition, we reported that ADI synergizes with Taxol in preclinical xenograft model. Based on this finding, a phaseI/II clinical trial is underway at UCD. Intriguingly, we found that ADI killing of cancer cells is associated with aggressive autophagy and appears to be caspase independent. At early phase, autophagy is protective and prolongs the survival of treated cells. Using high-resolution, live imaging, molecular and genetic profiling, we have now characterized in details the arginine-deprived cells undergoing apoptosis. The starved cells showed significant epigenetic reprogramming, excessive autophagy and most remarkably, nuclear rupture. The possible mechanism(s) and its implication will be discussed.

Session II

Cancer Metabolism and Signaling

Moderator:

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Recent Selected Publications

◎ Raskin L, Dakubo JC, Palaski N, Greenson JK, **Gruber SB**. (2013) Distinct molecular features of colorectal cancer in Ghana. *Cancer Epidemiol.* Oct;37(5):556-61.

◎ Raskin L, Fullen DR, Giordano TJ, Thomas DG, Frohm ML, Cha KB, Ahn J, Mukherjee B, Johnson TM, **Gruber S**B. (2013) Transcriptome profiling identifies HMGA2 as a biomarker of melanoma progression and prognosis. *J Invest Dermatol.* Nov;133(11):2585-92.

◎ Raymond VM, Mukherjee B, Wang F, Huang SC, Stoffel EM, Kastrinos F, Syngal S, Cooney KA, **Gruber SB**. (2013) Elevated risk of prostate cancer among men with Lynch syndrome. *J Clin Oncol.* May 10;31(14):1713-8.

◎ Samadder NJ, Gornick M, Everett J, Greenson JK, **Gruber SB.** (2013) Inflammatory bowel disease and familial adenomatous polyposis. *J Crohns Colitis.* Apr 1;7(3):e103-7.

◎ Raymond VM, Herron CM, Giordano TJ, **Gruber SB**. (2012) Familial renal cancer as an indicator of hereditary leiomyomatosis and renal cell cancer syndrome. *Fam Cancer.* Mar;11(1):115-21.

◎ Vilar E, Tabernero J, **Gruber SB**. (2011) Micromanaging the classification of colon cancer: the role of the microRNAome. *Clin Cancer Res*. Dec 1;17(23):7207-9.

◎ Gornick MC, Rennert G, Moreno V, **Gruber SB**. (2011) Adiponectin gene and risk of colorectal cancer. *Br J Cancer.* Aug 9;105(4):562-4.

◎ Jeter JM, Bonner JD, Johnson TM, **Gruber SB**. (2011) Nonsteroidal anti-inflammatory drugs and risk of melanoma. *J Skin Cancer.* 598571.

◎ Boonstra PS, Mukherjee B, Taylor JM, Nilbert M, Moreno V, **Gruber SB**. (2011) Bayesian modeling for genetic anticipation in presence of mutational heterogeneity: a case study in Lynch syndrome. *Biometrics.* Dec;67(4):1627-37.

◎ Samadder NJ, Mukherjee B, Huang SC, Ahn J, Rennert HS, Greenson JK, Rennert G, **Gruber SB**. (2011) Risk of colorectal cancer in self-reported inflammatory bowel disease and modification of risk by statin and NSAID use. *Cancer.* Apr 15;117(8):1640-8.

Molecular Pathways and Survival in Colorectal Cancer

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Colorectal cancers (CRC) display a large variety of somatic and germline genetic features that distinguish subsets of cancers with specific biologic behavior. Here we describe the results of a large, population-based study of 3,899 colorectal cancer cases and study these individuals to quantify CRC sub-types of clinical importance and to understand the relationships between molecular profiles and survival. Microsatellite instability, IHC expression of relevant MMR genes (MLH1, MSH2, MSH6, PMS2), founder and private germline mutations in the relevant genes and somatic mutations in the KRAS/BRAF or mTOR/PI3K signal transduction pathways all have potential prognostic and predictive implications and were assessed in tumor and germline DNA from all cases. Clinical and molecular annotation, combined with long term follow-up permitted multivariate survival analyses to identify the key molecular features associated with prognosis. Key findings will be presented.

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Recent Selected Publications

◎ **Lee, E. Y.-H. P** and Abbondante, S. (2014) Tissue-specific tumor suppression by BRCA1. *Proc. Natl. Acad. Sci.* 111:4353-4.

◎ Hu, C-M., Zhu, J., Guo, XE, Chen, W., Qiu, X., Ngo, B., Chien,R., Wang, Y.W., Tsai, C.Y., Wu, G., Kim, Y., Lopez, R., Chamberlin, R., **Lee, E. Y.-H. P.** and Lee, W-H. (2014) Novel small molecules disrupting Hec1/Nek2 interaction ablates tumor progression by triggering Nek2 degradation through a death-trap mechanism. *Oncogene.*

◎ Wang, S., Li, Y., Hsu, PH., Lee, SY, Kim, Y., and **Lee, E. Y.-H. P.** (2013) Down-regulation of GSK-3 contributes to stabilization of progesterone receptor A in the Brca1-deficiency mammary gland. *J. Biol. Chem.* 288:26265-71.

◎ Hwang-Verslues, WW., Chang, PH., Chang, Jeng, YM, Chiang, PH., Chang, YC, Hsieh, TH., Su, FY., Lin, LC., Abbondante, S., Yang, CY., Hsu, HM., Yi. JC., Chang, KJ, Shew, JY., **Lee, E. Y.-H. P.** and Lee, W.-H. (2013) Loss of corepressor PER2 under hypoxia upregulateds OCT-1 by de-repressing Oct1-mediated EMT gene expression. *Proc. Natl. Acad. Sci.* 110:12331-6.

◎ Hwang-Verslues, WW., Lee, WH. And **Lee, E. Y.-H. P.** (2012) Biomarkers to target heterogeneous breast cancer stem cells. *J. Mol. Biomarkers Diagn.*

◎ Dong, Y., Nakagawa-Goto, K., Lai, CY., Pan, SL., Morris-Natschke, SL., Bastow, KF, Kim, Y., Lee, **E. Y.-H. P,** Lee KH. (2012) Antitumor agents. 289. Design, synthesis, and anti-breast cancer activity in vivo of 4 – amino - 2H - benzo[h]chromen – 2 - one and 4 – amino -7,8,9,10-tetrahydro - 2H - benzo[h]chromen-2-one analogues with improved water solubility. *J Nat. Prod.* 75: 370-7.

◎ Tyan, SW., Kuo, WH., Huang, CK., Pan, CC., Shew, JY., Chang, KJ, **Lee, EYH P*** and Lee, WH*. (2011) Breast cancer cells induce cancer-associated fibroblasts to secrete hepatocyte growth factor to enhance breast tumorigenesis. *PLoS One* 6 (1):e15313.

◎ Usami, Y., Nakagawa-Goto, K., Lang, JY., Lai, CY., Goto, M., Sakurai, N., Taniguchi, M., Akiyama, T., Morris-Natschke, SL., Bastow, KF., Cragg, G., Newman, DJ., Fujitake, M., Takeya, K., Hung, MC., **Lee, E. Y.-H. P,** and Lee KH. (2010) Antitumor Agents 282.2′-(R)-O-Acetylglaucarubinone, a Quassinoid from Odyendyea gabonensis as a Potential Anti-breast and Anti-ovarian Cancer Agent. *J.Nat. Prod.* 73: 1553-8.

◎ **Lee, E. Y.-H. P.** and Muller WJ. (2010) Oncogenes and tumor suppressor genes. *Cold Spring Harb Perspect Biol*. 2(10): a003236.

◎ Dong, Y., Shi Q., Pai, HC., Peng, CY., Pan, SL., Teng, CM., Nakagawa-Goto, K, Yu., D, Liu, YN., Wu, PC., Bastow, KF, Morris-Natschke, SL., Brossi, A, Lang, JY, Hsu, JL., Hung, MC., **Lee, E. Y.-H. P**, Lee KH. (2010) Antitumor agents. 272. Structure-activity relationships and in vivo selective anti-breast cancer activity of novel neo-tanshinlactone analogues. *J Med Chem*. 53(5): 2299-308.

◎ Hwang-Verslues, WW., Kuo, WH., Chang, PH., Pan, CC., Wang, HH., Tsai, ST., Jeng, YM., Shew, JY., Kung, JT., Chen, CH., **Lee, E. Y.-H. P***., Chang, KJ*., Lee, WH*. (2009) Multiple lineages of human breast caner stem/progenitor cells identified with stem cell markers. *PLoS One* 4 (12): e8377.

Genetic and hormonal contribution in breast cancer: tissue-specific tumor suppression by BRCA1

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Both the genetic make up and the endocrine system play crucial roles in breast carcinogenesis. Germ-line mutation in the tumor suppressor gene *BRCA1* increases the lifetime risk for breast cancer and ovarian cancer by up to ~80% and ~50%, respectively. Population-based studies support a sex- and tissue-specific tumor suppressor function of BRCA1, but the mechanisms of this specificity are not fully understood. Somatic loss of the normal functioning allele in BRCA1 carriers is common in cancer development and additional somatic events, including mutations of PTEN and TP53, occur at high frequencies. Studies of these carriers have found that breast cancer onsets in recent generations occur at much younger ages.

BRCA1 is ubiquitously expressed and has been found to play important roles in DNA replication and repair, cell cycle checkpoint control, in addition to its activity as a transcriptional regulator. We have identified a connection of BRCA1 mutations and stabilization of progesterone receptor (PR) through various pathways and an increased sensitivity of Brca1 deficiency to progesterone-induced mammary epithelial proliferation. Circadian oscillation influences many biological functions including sleep cycles, hormone secretion and cellular metabolism. A central circadian player, period 2 (Per2), is down regulated in Brca1/p53-deficienct mammary epithelial cells. Furthermore, Per-2 represses the expression of a group of genes critical for tumor progression. We also found how oxygen levels control the abundance of Per2 protein. In addition to decreased Per-2, some other contributing factors leading to earlier breast cancer onsets will be presented.

Session III

Biomarker and Individualized Therapy in Cancer

Moderator:

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Recent Selected Publications

◎ Fu CH, Lin RJ, Yu J, Chang WW, Liao GS, Chang WY, Tseng LM, Tsai YF, Yu JC and **Yu AL***. (2014) SHIP2 plays an oncogenic role in breast cancer stem cells through JNK/vimentin activation and its phosphatase activity. *Stem Cell* (in press)

◎ Lin, JJ, Huang, CS, Yu, J, Liao, GS, Lien, HC, Hung, JT, Lin, RJ, Chou, FP, Yeh, KT and **Yu, AL***. (2014) Malignant phyllodes tumors display mesenchymal stem cell features and ALDH/GD2 identify their tumor stem cells. *Breast Cancer Research* 16: R29.

◎ Huang JR, Tsai YC, Chang YJ, Wu JC, Hung JT, Lin KH, Wong CH and **Yu AL***. (2014) α-GalCer but not phenyl-glycolipids induced : NKT cell anergy and IL-33 mediated MDSC accumulation via upregulation of egr2/3. *Journal of Immunology* 192: 1972-1981.

◎ Huang JR, Tsai YC, Chang YJ, Wu JC, Hung JT, Lin KH, Wong CH and **Yu AL***. (2013) α-GalCer but not phenyl-glycolipids induced NKT cell anergy and IL-33 mediated MDSC accumulation via upregulation of egr2/3. *Journal of Immunology* 192: 1972-1981

◎ Tsai YC, Huang JR, Cheng JY, Lin JJ, Hung JT, Wu YY, Yeh KT*, **Yu AL***. (2013) A prevalent cancer associated glycan, Globo H ceramide, induces immunosuppression by reducing Notch1 signaling Cancer Group. *J. Cancer Science & Therapy* 5: 264-270

◎ Chan YT, Lin YC, Lin RJ, Kuo HH, Thang WC, Chiu KP, **Yu AL***. (2013) Concordant and Discordant Regulation of Target Genes by miR-31 and Its Isoforms. *PLOS ONE* 8(3):e58169.

◎ Chang WW, Lin RJ, Yu J, Chang WY, Fu CH, Lai AC, Yu JC, **Yu AL**. (2013) The expression and significance of insulin-like growth factor-1 receptor and its pathway on breast cancer stem/progenitors. *Breast Cancer Res.* 12;15(3):R39.

◎ Unguru Y, Joffe S, Fernandez CV, **Yu AL***. (2013) Ethical Issues for Control-Arm Patients After Revelation of Benefits of Experimental Therapy: A Framework Modeled in Neuroblastoma. *J Clin Oncol.* 10; 31(5):641-6.

◎ Hsieh MH, Hung JT, Liw YW, Lu YJ, Wong CH, **Yu AL***, Liang PH. (2012) Synthesis and evaluation of acyl-chain- and galactose-6"-modified analogues of α-GalCer for NKT cell activation. *Chembiochem.* 13(11):1689-97.

Cancer immunotherapy targeting tumor-associated glycans

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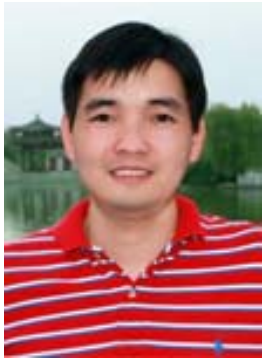
Aberrant glycosylation is a feature of cancer cells. GD2, a disialoganglioside, is highly expressed in neuroblastoma, melanoma and small cell lung cancer and some sarcomas. Dr. Yu has pursued immunotherapy of neuroblastoma with a monoclonal anti-GD2 antibody, ch14.18, from preclinical studies to IND, phase I through phase III studies. The pivotal international phase III randomized trial in high risk neuroblastoma culminated in demonstrating that immunotherapy with ch14.18 + cytokines improved event free survival significantly from 46%±5% to 66%±5% (p=0.012) and overall survival from 75%±5% to 86%±4% at 2 yrs (p=0.022). This is the first time that a glycan is shown to be an effective target for cancer immunotherapy.

Another prevalent cancer associated glycan is Globo H, a hexasaccharide identified as a ceramide-linked glycolipid. It is overexpressed in a variety of common cancers including colon, ovarian, gastric, pancreatic, lung, prostate and breast cancers, but not detectable or only weakly expressed in limited normal tissues. Thus, it is an ideal target for cancer immunotherapy. Dr. Yu's group found Globo H to be present in breast cancer stem cells (BCSCs), although to a much lesser extent than non-BCSCs, in clinical breast cancer specimens. They also provided the first evidence for the expression of Gb5, the pentasaccharide precursor of Globo H, in BCSCs of >60% of tumors. Immunization of mice with Globo H-KLH and adjuvant induced antibody reactive with not only Globo H but also Gb5, suggesting that Globo H-based immunotherapy will target Globo H and Gb5-expressing tumor cells. Recently, they have uncovered a new aspect of immunosuppressive effects of Globo H ceramide (GHCer) which facilitate the escape of cancer cells from immune surveillance. The molecular processes involve down-regulation of Notch1 signaling at transcriptional level by ID3, and protein level through egr2/3 controlled *itch* expression. These data support the notion that GHCer plays dual roles in serving as a cancer-associated antigen, and as an immune checkpoint, further propelling the ongoing multi-national phase II/III clinical trial of globo H vaccine in breast cancer. In the meantime, a new generation of Globo H vaccine has been generated in collaboration with Dr. Wong's group by conjugating Globo H to diphtheria toxoid as a carrier protein and use of C34, a new analog of alpha-galactosylceramide (α-GalCer), as an adjuvant. The latter is a superior over α-GalCer, as reflected by its lack of α-GalCer- induced anergy and accumulation of myloid dervived suppressor cells. Further details will be discussed.



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Recent Selected Publications

◎ Han, X., Li, F., Fang,Z., Gao, Y., Li, F., Fang,R., Yao,S., Sun,Y.,Li, L., Zhang, W., Ma,H., Xiao, Q., Ge, G., Fang,J., Wang,H., Zhang,L., Wong, K., Chen, H., Hou, Y., **Ji H***. (2014) Transdifferentiation of Lung Adenocarcinoma in mice with Lkb1 Deficiency to Squamous Cell Carcinoma. *Nat Commun*, doi: 10.1038/ncomms4261.

◎ Jiao S, Wang H, Shi Z, Dong A, Zhang W, Song X, He F, Wang Y, Zhang Z, Wang W, Wang X, Guo T, Li P, Zhao Y, **Ji H***, Zhang L*, Zhou Z*. (2014) A Peptide Mimicking VGLL4 Function Acts as a YAP Antagonist Therapy against Gastric Cancer. *Cancer Cell*. 25,166-180

◎ Zhang W, Gao Y, Li P, Shi Z, Guo T, Li F, Han X, Feng Y, Zheng C, Wang Z, Li F, Chen H, Zhou Z*, Zhang L*, **Ji H***. (2014) VGLL4 functions as a new tumor suppressor in lung cancer by negatively regulating the YAP-TEAD transcriptional complex. *Cell Res*, Jan 24. doi: 10.1038/cr.2014.10.

◎ Feng Y, Wang Y, Wang Z, Fang Z, Li F, Gao Y, Liu H, Xiao T, Li F, Zhou Y, Zhai Q, Liu X, Sun Y, Bardeesy N, Wong KK, Chen H, Xiong ZQ, **Ji H***. (2012) The CRTC1-NEDD9 signaling axis mediates lung cancer progression caused by LKB1 loss. *Cancer Res*. 72(24):6502-11.

◎ Li F, Feng Y, Fang R, Fang Z, Xia J, Han X, Chen H*, Liu H*, **Ji H***. (2012) Identification of RET gene fusion by exon array analyses in "pan-negative" lung cancer from never smokers. *Cell Res*. 22(5):928-31.

◎ Gao Y, Xiao Q, Ma H, Li L, Liu J, Feng Y, Fang Z, Wu J, Han X, Zhang J, Sun Y, Wu G, Padera R, Chen H, Wong KK, Ge G*, **Ji H***. (2010) LKB1 inhibits lung cancer progression through lysyl oxidase and extracellular matrix remodeling. *Proc Natl Acad Sci U S A.* 107(44):18892-7.

◎ Sun Y, Ren Y, Fang Z, Li C, Fang R, Gao B, Han X, Tian W, Pao W[#], Chen H[#], **Ji H**[#]. (2010) Lung adenocarcinoma from East asian never-smokers is a disease largely defined by targetable oncogenic mutant kinases. *J Clin Oncol*. 2010, 28, 4616-20. (# equal contribution)

◎ **Ji H**, Ramsey MR, Hayes DN, Fan C, McNamara K, Kozlowski P, Torrice C, Wu MC, Shimamura T, Perera SA, Liang MC, Cai D, Naumov GN, Bao L, Contreras CM, Li D, Chen L, Krishnamurthy J, Koivunen J, Chirieac LR, Padera RF, Bronson RT, Lindeman NI, Christiani DC, Lin X, Shapiro GI, Janne PA, Johnson BE, Meyerson M, Kwiatkowski DJ, Castrillon DH, Bardeesy N, Sharpless NE, Wong KK. (2007) LKB1 modulates lung cancer differentiation and metastasis. *Nature.* 448(7155):807-10.

◎ **Ji H**, Li D, Chen L, Shimamura T, Kobayashi S, McNamara K, Mahmood U, Mitchell A, Sun Y, Al-Hashem R, Chirieac L.R, Padera R, Bronson R. T, Kim W, Janne P.A, Shapiro G.I, Tenen D, Johnson B.E, Weissleder R, Sharpless N.E, Wong KK. (2006) The impact of human EGFR kinase domain mutations on lung tumorigenesis and in vivo sensitivity to EGFR targeted therapies. *Cancer Cell.* 9(6):485-95.

◎ **Ji H**, Zhao X, Yuza Y, Shimamura T, Li D, Protopopov A, Jung B.L, McNamara K, Xia H, Glatt K.A, Thomas R.K, Sasaki H, Horner J.W, Mitchell A, Sun Y, Al-Hashem R, Bronson R.T, Rabindran S.K, Discafani C.M, Maher E, Shapiro G.I, Meyerson M, Wong KK. (2006) Epidermal Growth Factor Receptor Variant III Mutations in Lung Tumorigenesis and Sensitivity to Tyrosine Kinase Inhibitors. *Proc Natl Acad Sci USA.* 103(20):7817-22.

YAP inhibits squamous transdifferentiation of Lkb1-deficient lung adenocarcinoma through DNp63 repression

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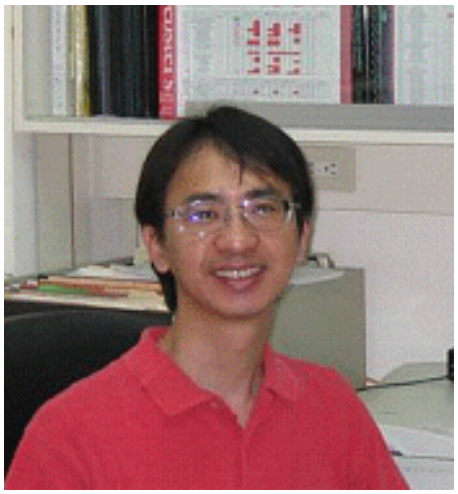
Whether Hippo pathway contributes to cell lineage transition under pathological conditions, especially tumorigenesis, remains largely unknown. Through integrative studies on mouse models, human cancer cell lines and clinical specimens, we here find a distinct YAP activation pattern in lung adenocarcinoma(ADC) and squamous cell carcinoma(SCC); YAP is initially activated by LKB1 loss in lung ADC which represses DNp63 transcription in a default manner. During transdifferentiation, YAP is inactivated which in turn mediates default repression of DNp63 and triggers squamous differentiation reprogramming. Disruption of the YAP barrier for phenotypic transition significantly accelerates squamous transdifferentiation; constitutive activation of YAP conversely inhibits this transition. More importantly, ectopic DNp63 expression rescues the inhibitory effect of YAP upon squamous transdifferentiation. These findings have established YAP as an essential barrier for lung cancer cell fate conversion and provided a novel mechanism in phenotypic plasticity, which might hold important implication for YAP-targeted therapies.

Session III

Biomarker and Individualized Therapy in Cancer

Moderator:



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Recent Selected Publications

◎ Hua KT, Tan CT, Johansson G, Lee JM, Yang PW, Lu HY, Chen CK, Su JL, Chen PB, Wu YL, Chi CC, Kao HJ, Shih HJ, Chen MW, Chien MH, Chen PS, Lee WJ, Cheng TY, Rosenberger G, Chai CY, Yang CJ, Huang MS, Lai TC, Chou TY, Hsiao M, **Kuo ML**. (2011) N-α-acetyltransferase 10 protein suppresses cancer cell metastasis by binding PIX proteins and inhibiting Cdc42/Rac1 activity. *Cancer Cell.* 19(2):218-31.

◎ Yen ML, Hou CH, Peng KY, Tseng PC, Jiang SS, Shun CT, Chen YC, **Kuo ML** (2011) Efficient derivation and concise gene expression profiling of human embryonic stem cell-derived mesenchymal progenitors. *Cell Transplant* 20(10):1529-45.

◎ Lin BR, Chang CC, Chen RJ, Jeng YM, Liang JT, Lee PH, Chang KJ, **Kuo ML** (2011)Connective tissue growth factor acts as a therapeutic agent and predictor for peritoneal carcinomatosis of colorectal cancer. *Clin Cancer Res.* 17(10):3077-88.

◎ Chen PS, Su JL, Cha ST, Tarn WY, Wang MY, Hsu HC, Lin MT, Chu CY, Hua KT, Chen CN, Kuo TC, Chang KJ, Hsiao M, Chang YW, Chen JS, Yang PC, **Kuo ML** (2011)miR-107 promotes tumor progression by targeting the let-7 microRNA in mice and humans. *J Clin Invest.* 121(9):3442-55.

◎ Cha ST, Chen PS, Johansson G, Chu CY, Wang MY, Jeng YM, Yu SL, Chen JS, Chang KJ, Jee SH, Tan CT, Lin MT, **Kuo ML**.(2010) MicroRNA-519c suppresses hypoxia-inducible factor-1alpha expression and tumor angiogenesis*Cancer Res.* 70(7):2675-85.

◎ Chen MW, Hua KT, Kao HJ, Chi CC, Wei LH, Johansson G, Shiah SG, Chen PS, Jeng YM, Cheng TY, Lai TC, Chang JS, Jan YH, Chien MH, Yang CJ, Huang MS, Hsiao M, **Kuo ML** (2010) H3K9 histone methyltransferase G9a promotes lung cancer invasion and metastasis by silencing the cell adhesion molecule Ep-CAM. *Cancer Res.* 70(20):7830-40.

◎ Chu CY, Cha ST, Lin WC, Lu PH, Tan CT, Chang CC, Lin BR, Jee SH, **Kuo ML** (2009) Stromal cell-derived factor-1alpha (SDF-1alpha/CXCL12)-enhanced angiogenesis of human basal cell carcinoma cells involves ERK1/2-NF-kappaB/interleukin-6 pathway.*Carcinogenesis.* 30(2):205-13.

◎ Wang MY, Chen PS, Prakash E, Hsu HC, Huang HY, Lin MT, Chang KJ, **Kuo ML** (2009) Connective tissue growth factor confers drug resistance in breast cancer through concomitant up-regulation of Bcl-xL and cIAP1.*Cancer Res.* 69(8):3482-91.

◎ Chien MH, Ku CC, Johansson G, Chen MW, Hsiao M, Su JL, Inoue H, Hua KT, Wei LH, **Kuo ML**. (2009) Vascular endothelial growth factor-C (VEGF-C) promotes angiogenesis by induction of COX-2 in leukemic cells via the VEGF-R3/JNK/AP-1 pathway. *Carcinogenesis.* 30(12):2005-13.

◎ Chu CY, Chang CC, Prakash E, **Kuo ML**. (2008) Connective tissue growth factor (CTGF) and cancer progression. *J Biomed Sci.* 15(6):675-85.

A novel therapeutic target for treating hepatocellular carcinoma by suppression vascular invasion and metastasis.

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Intra-hepatic vascular invasion of hepatocellular carcinoma (HCC) is the most important contributing factor to high recurrence and poor survival of patients. Here, we have identified leukocyte cell-derived chemotoxin 2 (LECT2) as a tumor suppressor that regulates hepatocellular carcinoma (HCC) vascular invasion and metastasis. LECT2 was inversely correlated with HCC recurrence and overall survival, and the expression of LECT2 was particularly high in non-vascular invasive samples. Furthermore, we employ a LECT2-affinity column plus LC-ms/ms to identify LECT2-binding proteins and found that MET receptor is strongly interacted with LECT2 protein. Despite the presence of HGF, the LECT2 binding causes an antagonistic effect to MET receptor activation through recruiting protein tyrosine phosphatase 1B (PTP1B). The antagonistic effect of LECT2 on MET activation also mainly contributes to the blockage of vascular invasion and metastasis of HCC. Our findings reveal a novel and specific inhibitory function of LECT2 in HCC via the direct binding and inactivation of MET, opening a potential avenue for treating MET-related cancer.

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Recent Selected Publications

◎ Liu Z, Chen P, Gao H, Ji H, Finley D, **Hu R***. Ubiquitylation of Optineurin activates selective autophagy for tumor suppression. ***Cancer Cell.*** (In press)

◎ Yu T., Zhang, Y., **Hu R.G***. (2014) Profiling human protein degradome delineates cellular responses to proteasomal inhibition and reveals a feedback mechanism in regulating proteasome homeostasis. *Cell Research* (In press)

◎ Shen J., Sheng X.P., Huang Y., **Hu R.G***. (2014) Iron Metabolism regualtes p53 signaling through direct heme-p53 interaction and modulation of p53 function, stability and localization. *Cell Reports.* 7:1-14. (Highlighted in "Faculty of 1000", and "Chemistry & Biology".)

◎ Xu X., Tao Y.H., Jing N., **Hu R.G***. (2014) ZIPseq: genome-wide mapping of DNA repeats at single base resolution. *Journal of Molecular and Cell Biology.* 6:93-6.

◎ Shen J., Song G., Hu J., **Hu R.G***. (2014) The use of hollow mesoporous silica nanospheres to encapsulate bortezomib and improve efficacy for non small cell lung cancer therapy. *Biomaterials.* 35(1):316-26

◎ Song G., Li C., Hu J., Zou R., Xu K., Han L., Yang J., Chen Z., Qin Z., Ruan K., **Hu R.G***. (2012) A simple transformation from silica core–shell–shell to yolk–shellnanostructures: a useful platform for effective cell imaging and drug delivery. *J. Mater. Chem.* 22: 17011-18

◎ **Hu R.G.,** Wang H., Varshavsky, A. (2008) The N-end rule pathway is a sensor of heme, *Proc. Natl. Acad. Sci. USA . 105(1):76-81.* (Highlighted in "Faculty of 1000")

◎ **Hu R.G.**, Brower, C. S., Wang, H., Davydov, I. V., Zhou, J., Kwon, Y. T. and Varshavsky, A. (2006) Arginyl-transferase, its specificity, putative substrates, bidirectional promoter, and splicing-derived isoforms. *J. Biol. Chem.* 281(43): 32559-73.

◎ **Hu R.G.**, Sheng J., Qi X., Xu Z., Takahashi T.T. and Varshavsky A., (2005) The N-end rule as a nitric oxide (NO) sensor, controlling the levels of multiple regulators, *Nature*. 437(7061):981-6. (Highlighted in Nature Review Mol .Cell Biology 2005, 6: 822-823; Faculty of 1000; Journal of Cell Biology, 2005, 171: 406-407; Science STKE, Vol. 2005, 306: tw362;, Nature AFCS, 2005 feature article.)

Iron metabolism regulates p53 signaling through direct heme-p53 interaction and modulating localization, stability and function of p53

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Iron excess is closely associated with tumorigenesis in multiple types of human cancers, with underlying mechanisms yet unclear. Recently, iron deprivation has emerged as a major strategy for chemotherapy, but it exerts tumor-suppression only on select human malignancies. Here, we report that tumor suppressor p53 protein (p53) is downregulated during iron excess. Strikingly, heme, the iron polyporphyrin, binds to p53 protein, interferes with p53-DNA interactions and triggers nuclear export of p53 followed by cytosolic degradation. Moreover, in a tumorigenicity assay, iron deprivation suppressed tumor growth largely with dependence on wild-type p53, suggesting that upregulation of wild-type p53 signaling might critically underlie the selective efficacy of iron deprivation. Our findings thus identify the first direct link between iron/heme homeostasis and the regulation of p53 signaling, which not only provides mechanistic insights on tumorigenesis associated with iron excess, but may also help predict and improve outcomes in iron-deprivation based chemotherapy.

Session IV

Chromosome Instability in Cancer Development (II)

Moderator:

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Astrid Gräslund, Ph.D.

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Professor and Chairman
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Recent Selected Publications (Selected from >300 peer-reviewed publications):

◎ Hammerstad M, Røhr AK, Andersen NH, **Gräslund A**, Högbom M, Andersson KK (2014) The class Ib ribonucleotide reductase from Mycobacterium tuberculosis has two active R2F subunits. J Biol Inorg Chem. Mar 2. [Epub ahead of print]

◎ Björnerås J, Kurnik M, Oliveberg M, **Gräslund A**, Mäler L, Danielsson J. (2014) Direct detection of neuropeptide dynorphin a binding to the second extracellular loop of the κ opioid receptor using a soluble protein scaffold. FEBS J. 281(3):814-24.

◎ Wang C, Klechikov AG, Gharibyan AL, Wärmländer SK, Jarvet J, Zhao L, Jia X, Shankar SK, Olofsson A, Brännström T, Mu Y, **Gräslund A**, Morozova-Roche LA. (2014) The role of pro-inflammatory S100A9 in Alzheimer's disease amyloid-neuroinflammatory cascade. Acta Neuropathol. 127(4):507-22.

◎ Luo J, Otero JM, Yu CH, Wärmländer SK, **Gräslund A**, Overhand M, Abrahams JP. (2013) Inhibiting and reversing amyloid-β peptide (1-40) fibril formation with Gramicidin S and engineered analogues. Chemistry. 16;19(51):17338-48.

◎ Dobrov A, Göschl S, Jakupec MA, Popović-Bijelić A, **Gräslund A**, Rapta P, Arion VB (2013) A highly cytotoxic modified paullone ligand bearing a TEMPO free-radical unit and its copper(ii) complex as potential hR2 RNR inhibitors. Chem Commun (Camb). 49(85):10007-9.

◎ Mitsueda A, Shimatani Y, Ito M, Ohgita T, Yamada A, Hama S, **Gräslund A**, Lindberg S, Langel U, Harashima H, Nakase I, Futaki S, Kogure K (2013) Development of a novel nanoparticle by dual modification with the pluripotential cell-penetrating peptide PepFect6 for cellular uptake, endosomal escape, and decondensation of an siRNA core complex. Biopolymers. 100(6):698-704.

◎ Griese JJ, Roos K, Cox N, Shafaat HS, Branca RM, Lehtiö J, **Gräslund A**, Lubitz W, Siegbahn PE, Högbom M. (2013) Direct observation of structurally encoded metal discrimination and ether bond formation in a heterodinuclear metalloprotein. Proc Natl Acad Sci U S A. 2013 Oct 22;110(43):17189-94.

◎ Abelein A, Kaspersen JD, Nielsen SB, Jensen GV, Christiansen G, Pedersen JS, Danielsson J, Otzen DE, **Gräslund A**. (2013) Formation of dynamic soluble surfactant-induced amyloid β peptide aggregation intermediates. J Biol Chem. 288(32):23518-28.

◎ Luo J, Wärmländer SK, **Gräslund A**, Abrahams JP. (2013) Human lysozyme inhibits the in vitro aggregation of Aβ peptides, which in vivo are associated with Alzheimer's disease. Chem Commun (Camb). 49(58):6507-9.

◎ Björnerås J, **Gräslund A**, Mäler L. (2013) Membrane interaction of disease-related dynorphin A variants. Biochemistry. 52(24):4157-67.

◎ Sigfridsson KG, Chernev P, Leidel N, Popovic-Bijelic A, **Gräslund A**, Haumann M. (2013) Rapid X-ray photoreduction of dimetal-oxygen cofactors in ribonucleotide reductase. J Biol Chem. 288(14):9648-61.

◎ Madani F, Abdo R, Lindberg S, Hirose H, Futaki S, Langel U, **Gräslund A**. (2013) Modeling the endosomal escape of cell-penetrating peptides using a transmembrane pH gradient. *Biochim Biophys Acta.* 1828(4):1198-204.

Ribonucleotide reductase- a dimetal/tyrosyl free radical enzyme

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Transition metal ions like iron and manganese are important components of many enzymes. Diiron carboxylate enzymes are well-known participants in challenging redox reactions. Bacterial multicomponent monooxygenases and protein R2 of class I ribonucleotide reductase (RNR) are typical examples of such proteins.

In mammalian RNRs the enzymatic reaction is a bottleneck for providing the deoxyribonucleotide building blocks for DNA synthesis, both for DNA replication and repair. The mammalian class Ia RNR enzyme has two subunits, named proteins R1 and R2. The enzyme reduction reaction takes place in protein R1, but the activation of the enzyme depends on the diiron/tyrosyl free radical cluster in protein R2. The formation of the stable free radical on a tyrosine residue is a metal/oxygen dependent redox reaction. A long range proton coupled electron transfer (PCET) connects the radical site in R2 to the substrate binding site in R1.

Several inhibitors of the RNR enzyme, based on destruction of the stable tyrosyl free radical, have been identified. One such class of inhibitors is based on the activities of metal complexes of thiosemicarbazones (1).

Some years ago, a new class (Ic) of RNRs was identified in *Chlamydia trachomatis* (2). Electron Paramagnetic Resonance (EPR) spectroscopy studies showed that it lacks the tyrosyl radical found in other class I RNRs. As a metal cofactor this enzyme has a manganese/iron cluster instead of the common diiron cluster found in class Ia RNRs.

In class Ic RNR, the manganese/iron cluster has a similar function as the tyrosyl radical found in the R2 proteins of other class I RNRs. This function is to provide a shielded, reversible electron storage site during the enzymatic reaction, when the reduction of ribonucleotides takes place at the active site about 35Å away in protein R1.

The formation and catalytic activities of the manganese/iron cluster in this enzyme, as well as the EPR spectroscopic properties, have been characterized.

References:

1. Popovic-Bijelic A, Kowol C, Lind M., Luo J, Himo F., Enyedy E, Arion V, Gräslund A. (2011) J. Inorg. Biochem. 105: 1422-1431.

2. Högbom M, Stenmark P, Voevodskaya N, McClarty G, Gräslund A, Nordlund P (2004) Science 305:245-24; Voevodskaya N, Lendzian F, Ehrenberg A, Gräslund A (2007) FEBS Lett. 581:3351-3355; Popovic-Bijelic A, Voevodskaya N, Domkin V, Thelander L, Gräslund A (2009) Biochemistry 48:6532-6539.

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Recent Selected Publications

◎ Hammerstad M., H.-P. Hersleth, A.B.Tomter, Å.K. Røhr and **K.K. Andersson** (2014) Crystal Structure of *Bacillus cereus* Class Ib Ribonucleotide Reductase Di-iron NrdF in Complex with NrdI. *ACS Chem. Biol.* **9**, 526-537.

◎ Rackwitz S., I. Faus, M. Schmitz, H.-J. Krüger, **K.K. Andersson**, H.-P. Hersleth, K. Achterhold, K. Schlage, H.-C. Wille, V. Schünemann, and J.A. Wolny (2014) A New Sample Environment for Cryogenic Nuclear Resonance Scattering Experiments on Single Crystals and Microsamples at P01, PETRA III. *Hyperfine Interactions* (in press)

◎ Hammerstad M., Å.K. Røhr, N.H. Andersen, A. Gräslund, M. Högbom, and **K.K. Andersson** (2014) The Class Ib ribonucleotide reductase from *Mycobacterium tuberculosis* has Two Active R2F Subunits. *J. Biol. Inorg. Chem.* in press.

◎ Forsberg Z., Å.K. Røhr, S. Mekasha, **K.K. Andersson**, V.G.H. Eijsink, G. Vaaje-Kolstad, and M. Sørlie (2014) Comparative study of two chitin-active and two cellulose-active AA10-type lytic polysaccharide *Biochemistry* in press.

◎ Tomter, A.B., G. Zoppellaro, N.H. Andersen, H.-P. Hersleth, M. Hammerstad, Å.K. Røhr, G.K. Sandvik, K.R. Strand, G.E. Nilsson, C.B. Bell III, A.-L. Barra, E. Blasco, L. Le Pape, E.I. Solomon, and **K.K. Andersson** (2013) Ribonucleotide reductase class I with different radical generating clusters. *Coord. Chem. Rev*. 257, 3-26.

◎ Can M., J. Krucinska, G. Zoppellaro, N.H. Andersen, J.E. Wedekind, H.-P. Hersleth, **K.K. Andersson** and K.L. Bren (2013) Structural characterization of *Nitrosomonas europaea* cytochrome c_{552} variants with marked differences in electronic structure. *ChemBioChem* ***14,*** 1828 – 1838.

◎ Røhr Å.K., M. Hammerstad and **K.K. Andersson** (2013) Stabilization of two nucleophilic cysteines thiolates in the active site of the BC3987 thioredoxin. *PLoS ONE.* 8(7): e69411.

◎ Zhao X., H.-P. Hersleth, J. Zhu, **K.K. Andersson** and R.S. Magliozzo (2013) Access channel residues Ser315 and Asp137 in *Mycobacterium tuberculosis* catalase-peroxidase (KatG) control activation of the pro-drug isoniazid. *Chem. Commun*. **49**, 11650-11652.

◎ Tomter, A.B., G. Zoppellaro, C.B. Bell III, A.-L. Barra, N.H. Andersen, E.I. Solomon, and **K.K. Andersson** (2012) Spectroscopic Studies of the Iron- and Manganese Reconstituted Tyrosyl Radical in *Bacillus cereus* Ribonucleotide Reductase R2 Protein. *PloS ONE* 7 (3), e33436.

◎ Sandvik G.K., A.B.Tomter, J. Bergan, G. Zoppellaro, A.-L. Barra, Å.K. Røhr, M. Kolberg, S. Ellefsen, **K.K. Andersson**, and G.E. Nilsson (2012) Studies of Ribonucleotide Reductase in Crucian Carp - An Oxygen Dependent Enzyme in an Anoxia Tolerant Vertebrate. *PloS ONE*, 8 (7) e42784.

◎ Andersson, K.K. (2012) Symposium on enzymet Ribonukleotidreduktase i Philadelphia. *NBS-nytt 2012*, (1), 23-23.

◎ Bakke, O., and **K.K. Andersson**(2012) Åpent seminar: Fra imaging show til celler og proteinsrukturer. *NBS-nytt 2012,* (1), 22-22.

Studies of the NrdF-NrdI complex and different metal ion clusters in class I ribonucleotide reductases

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Oxygen dependent ribonucleotide reductase (RNR) catalyzes the conversion of ribonucleotides to deoxyribonucleotides. The class Ia and Ib small subunit R2 carries a stable tyrosyl radical which is necessary for enzymatic activity[1]. We have studied the class Ib RNR R2F enzyme from Bacillus cereus, an opportunistic pathogen causing food poisoning, by light absorption, EPR, HF-EPR, CD, Raman, magnetic circular dicroism (MCD), and VTVH-MCD spectroscopy[2,3], in addition to 3D-structures obtained by protein crystallography of a R2F-NrdI complex[4]. We have also analyzed four different tyrosyl radicals from class Ia RNR from an anoxia tolerant carp[5] and one from Epstein-Barr virus[6]. In R2/R2F radicals, differences can be seen in rotational conformation of the phenoxyl rings and the presence of hydrogen bonds to phenyl-oxygens. We observed a tyrosyl-radical interacting with a di-manganese cluster in B. cereus R2F formed with the help of NrdI[7], similar to other class Ib R2Fs[8,9]. The manganese R2F has higher specific activity than the iron form with a thioredoxin reductant[10,11]. It seems we can obtain a tyrosyl radical interacting magnetically with other metal ions as well, such as Co(II). In the 3D-structure of iron-R2F-NrdI complex in B. cereus, we observe differences in the metal ion coordination site, as compared to the E. coli manganese-R2F-NrdI complex[4]. Interestingly, mammalian RNRs have both one R2 and one p53R2, carp RNR has two R2s and two p53R2s[5], while some bacteria can have two different R2Fs[12].

References;

[1] K. Kristoffer Andersson (Ed.), Ribonucleotide reductase, 2008, Nova Science Publishers Inc. Hauppauge, N.Y. USA ISBN: 978-1-60456-199-9;
[2] Tomter, et al. PLoS ONE 2012, 7, e33436;
[3] Tomter, et al. Coordin. Chem. Rev. 2013, 257, 3-26;
[4] Hammerstad, et al., ACS Chem. Biol. 2014, 9, 526-537;
[5] Sandvik, et al. PLoS ONE. 2012, 8, e42784;
[6] Tomter, et al., PloS ONE 2011, 6, e25022;
[7] Røhr et al., Angew. Chem. Int. Ed. 2010, 49, 2324;
[8] Cortruvo and J. Stubbe, Biochemistry 2010, 49, 1297;
[9] Cox et al., J. Am. Chem. Soc. 2010, 132, 11197;
[10] Crona et al, J. Biol. Chem. 2011, 286, 33053;
[11] Røhr et al., PloS ONE , 2013, 8(7): e69411;
[12] Hammerstad et al., J. Biol. Inorg. Chem. DOI: 10.1007/s00775-014-1121-x

Session IV

Chromosome Instability in Cancer Development (II)

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Recent Selected Publications (Selected from >300 peer-reviewed publications):

◎ Huang CCF, Weng JH, Wei TYW, Wu PTG, Hsu PH, Chen YH, Wang SC, Qin D, Hung CC, Chen ST, Wang AHJ, Shyy JYJ, and **Tsai MD** (2012) Intermolecular binding between TIFA-FHA and TIFA-pT mediates TNFα stimulation and NF-κB activation. Mol. Cell Biol. 32, 2664-2673.

◎ Wu HH, Wu PY, Huang KF, Kao YY, and **Tsai MD** (2012) Structural delineation of MDC1 FHA domain binding with CHK2 pThr68. Biochemistry 51, 575-577.

◎ Shen YF, Chen YH, Chu SY, Lin MI, Hsu HT, Wu PY, Wu CJ, Liu HW, Lin FY, Lin G, Hsu PH, Yang AS, Cheng YS, Wu YT, Wong CH, **Tsai MD** (2011) E339…R416 salt bridge of nucleoprotein as a feasible target for influenza virus inhibitors. Proc. Natl. Acad. Sci. USA 108, 16515-16520 (2011).

◎ Balbo PB, Wang ECW, and **Tsai MD** (2011) Kinetic mechanism of active site assembly and chemical catalysis of DNA Polymerase. Biochemistry 50, 9865-9875.

◎ Li J, Poi MJ, and **Tsai MD** (2011) The Regulatory Mechanisms of Tumor Suppressor P16INK4A and Relevance to Cancer. Biochemistry 50, 5566-5582. (Review)

◎ HoJH, Lin TL, Li CY, Lee A, Cheng AN, Chen MC, Wu SH, Wang JT, Li TL, and **Tsai MD** (2011) Functions of some capsular polysaccharide biosynthetic genes in Klebsiella pneumonia NTUH K-2044. PLoS One, 6, e21664.

◎ Bakhtina M, Roettger MP, and **Tsai MD** (2009) Contribution of the Reverse Rate of the Confor mational Step to Polymerase Fidelity. Biochemistry 48, 3197-3208.

◎ Mahajan A, Yuan C, Lee H, Chen ESW, Wu PY, and **Tsai MD** (2008) Structure and Function of the Phosphothreonine-Specific FHA Domain. Science Signaling 1, re12. (Review)

◎ Roettger MP, Bakhtina M, and **Tsai MD** (2008) Mismatched and Matched dNTP Incorporation by DNA Polymerase β Proceed via Analogous Kinetic Pathways. Biochemistry 47, 9718-9727.

◎ Kumar S, Bakhtina M, and **Tsai MD** (2008) Altered Order of Substrate Binding by DNA Polymerase X from African Swine Fever Virus. Biochemistry 47, 7875-7887.

◎ Lee H, Yuan C, HammeT A , Mahajan A, Chen ESW, Wu MR, Su MI, Heierhorst J, **Tsai MD** (2008) Diphosphothreonine-specific interaction between SQ/TQ cluster and an FHA domain in the Rad53-Dun1 kinase cascade. Mol. Cell 30, 767-778.

◎ Tang KH and **Tsai MD** (2008) Structure and Function of 2:1 DNA Polymerase·DNA Complexes. J. Cellular Physiology 216, 315-320. (Review)

◎ Tang KH, Niebuhr M, Tung CS, Chan HC, Chou CC, and **Tsai MD** (2008) Mismatched dNTP Incorporation by DNA Polymerase. Does Not Proceed via Globally Different Conformational Pathways. Nucleic Acids Res. 36, 2948-2957.

◎ Tang KH, Niebuhr M, Aulabaugh A, and **Tsai MD** (2008) Solution Structures of 2:1 and 1:1 DNA Polymerase-DNA Complexes Probed by Ultracentrifugation and Small-Angle X-ray Scattering. Nucleic Acids Res. 36, 849-860.

Structural approach to tumor suppressors and cancer signaling

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In this lecture I will present the use of structures to understand cancer signaling and DNA damage responses, on several subjects: the p16 family of tumor suppressor and their mutants identified in cancers; the histone demethylase RBP2; the tumor proliferation marker protein Ki67 and its binding with NIFK; the activation mechanism of human CHK2 and its yeast homolog Rad53 kinase. The role of FHA domain binding with phosphothreonine in the cancer related signaling and DNA damage responses will also be highlighted.

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Recent Selected Publications

◎ Wu J*, **Jiang H***, Luo S, Zhang M, Zhang Y, Sun F, Huang S, Li H. (2013) Caspase-mediated cleavage of C53/LZAP protein causes abnormal microtubule bundling and rupture of the nuclear envelope. *Cell Res. 23(5):691-704.* (* equal contribution)

◎ **Jiang H**, Pritchard JR, Williams RT, Lauffenburger DA and Hemann MT. (2011) A mammalian functional-genetic approach to characterizing cancer therapeutics. *Nat Chem Biol.* 7(2):92-100.

◎ Reinhardt HC*, **Jiang H***, Hemann MT and Yaffe MB. (2009) Exploiting synthetic lethal interactions for targeted cancer therapy. *Cell Cycle* 8(19):3112-9.

◎ **Jiang H***, Reinhardt HC*, Bartkova J, Tommiska J, Blomqvist C, Nevanlinna H, Bartek J, Yaffe MB and Hemann MT. (2009) The combined status of ATM and p53 link tumor development with therapeutic response. *Genes Dev.* 23(16):1895-909.

◎ **Jiang H***, Wu J*, He C, Yang W and Li H. (2009) Tumor suppressor protein C53 antagonizes checkpoint kinases to promote cyclin-dependent kinase 1 activation. *Cell Res.* 19(4):458-68.

◎ **Jiang H**, Luo S and Li H. (2005) Cdk5 activator-binding protein C53 regulates apoptosis induced by genotoxic stress via modulating the G2/M DNA damage checkpoint. *J. Biol.Chem.* 280: 20651-9

Probing drug vulnerability associated with recurrent cancer genetic lesions

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Biomarkers that predict cancer cell's resistance or sensitivity to various drugs are essential for developing new anticancer drugs as well as designing personalized cancer treatment. Until now, most clinically relevant biomarkers are based on common oncogenes and tumor suppressors. Mutations of these genes have major impact on cancer cells, changing the gene expression profiles, signaling cascades and stress response, which can greatly influence their response to drugs. On the other hand, these genes are recurrently mutated in cancers to a certain rate, making it feasible to stratify cancer patients according to the status of these genes.

A common method of studying cancer mutation associated drug vulnerability is to subject a large panel of human cancer cell lines to genetic and drug sensitivity profiling. Through complicated bioinformatics analysis, drug sensitivities are assigned to certain genetic lesions. However, due to the complex nature of human cancer cell lines and high variability of drug sensitivity data, these approaches have recently been proven ineffective as means to study cancer mutation-associated drug vulnerability. Here we present a simpler yet reliable system to probe the genetic interactions between deregulated cancer genes and anticancer drugs. We will discuss how eipigenetic regulators recurrently mutated in human cancers might dictate drug response.

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Recent Selected Publications

◎ Tien SC, and **Chang ZF** (2013) Oncogenic Shp2 disturbs microtubule regulation to cause HDAC6-dependent ERK hyperactivation. *Oncogene* Jun 17. [Epub ahead of print]

◎ Hu CC, Yeh, MT, Chen CW, Tsao N, Gao, QZ, Chang, CY, Lee MH, Fang JM, Sheu SY and Lin CJ, Tseng MC, Chen YJ, **Chang ZF**. (2012) Tumor cells require thymidylate kinase to prevent dUTP incorporation during DNA repair. *Cancer Cell* 22, 36-50.

◎ Chuang HH, Yang CH, Tsay YG, Hsu CY, Tseng LM, **Chang ZF**, Lee HH. (2012) ROCKII serine 1366 phosphorylation reflects the activation status. *Biochem. J.* 443: 145-151.

◎ Lee, HH, Tien, SC, Jou, TS, Chang, YC, Jhong, JG, Chang, ZF (2010) Src-dependent phosphorylation of ROCK participates in regulation of focal adhesion dynamics. *J Cell Sci.* 123:3368-77.

◎ Chen, YL., Eriksson, S., and Chang, ZF. (2010) The regulation and functional contribution of thymidine kinase 1 in repair of DNA damage. *J. Biol. Chem.* 285(35):27327-35.

◎ Chang YC, Tien SC, Tien HF, Zhang H, Bokoch GM and **Chang ZF** (2009) p210Bcr_Abl desensitizes Cdc42 GTPase signaling for SDF-1a-directed migration in chronic myeloid leukemia cells. *Oncogene*. 28:4105-15.

◎ Lee HH and **Chang ZF** (2008) Regulation of RhoA-dependent ROCK activation by Shp2. *J. Cell Biol.* 181:999-1012.

◎ Hu CM and **Chang ZF** (2008) Synthetic lethality by lentiviral short hairpin RNA silencing of thymidylate kinase and doxorubicin in colon cancer cells regardless of the *p53* status. *Cancer Res.* 68:2831-40.

◎ Ke PY, Hu CM., Chang YC, and **Chang ZF** (2007) Hiding human thymidine kinase 1 from APC/C-mediated destruction by thymidine binding. *FASEB J.* 21:2176-84.

◎ Kuo YY, and **Chang ZF (2007)** GATA-1 and Gfi-1B interplay to regulate Bcl-xL transcription. *Mol Cell Biol.* 27:4261-72.

◎ Chou WL, Chuang LM, Chou CC, Wang AHJ, Lawson JA, FitzGerald, GA and **Chang ZF** (2007) Identification of a novel prostaglandin reductase reveals the involvement of prostaglandin E2 catabolism in regulation of peroxisome proliferator-activated receptor gamma activation. *J Biol Chem.* 282:18162-72.

◎ Chang YC, Lee HH, Chen YJ, Bokoch GM, and **Chang ZF** (2006) Contribution of guanine exchange factor H1 in phorbol ester-induced apoptosis. *Cell Death Diff.* 13: 2023-32.

◎ Ke PY, Kuo YY, Hu CC and **Chang ZF** (2005) Control of dTTP pool size by anaphase promoting complex/cyclosome is essential for maintenance of genomic stability. *Genes Dev.* 19:1920-33.

◎ Ke PY and **Chang ZF** (2004) Mitotic degradation of human thymidine kinase 1 is dependent on the anaphase-promoting complex/cyclosome-CDH1-mediated pathway. *Mol Cell Biol.* 24:514-26.

Ribonucleotide reductase promotes the progression of genome instability via dUTP-mediated replication stress

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The increase in RRM2A subunit of ribonucleotide reductase (RNR) expression is oncogenic and is closely associated with human cancers. It is unknown whether other nucleotide metabolic enzyme can counteract the oncogenic function of RNR. Overexpression of RRM2A is sufficient to induce replication stress, DNA damage signal and chromosome aberrations in mitosis, all of which are prevented by coexpression of dUTPase. Our mechanistic study showed that RRM2 overexpression increases the breaks in AT-rich fragile sites. Data from DNA fiber analysis revealed that elevation of RRM2A increases the rate of replication forks while impeding replication restart. Exogenous addition of thymidine or knockdown of uracil DNA glycosylase abolishes RRM2-induced aberration in replication restart, suggesting the implication of dUTP incorporation. In cancer cells, the context of high RRM2/low dUTPase exhibited higher level of DNA damage signal, and the clone evolved to metastasize with better growth fitness contains high RRM2/high dUTPase. Thus, high RRM2/low dUTPase might confer a cellular context promoting cancer evolution in preneoplasias and tumor tissues. In agreement, analysis of clinical samples also demonstrated that RRM2A interplays with dUTPase to affect colon and breast cancer survival.

Student Forum

Moderator:

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Session V

Stem Cell Research in Cancer

Moderator:

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Recent Selected Publications

◎ Zhang Z, Lv X, Yin WC, Zhang X, Feng J, Wu W, Hui CC, Zhang L#, and **Zhao Y**#. (2013) Ter94 ATPase complex targets K11-linked ubiquitinated Ci to proteasomes for partial degradation. *Dev Cell,* 25:636-644.

◎ Zhang Z, Feng J, Pan C, Lv X, Wu W, Zhou Z, Liu F, Zhang L#, and **Zhao Y**#. (2013) Atrophin-Rpd3 complex represses Hedgehog signaling by acting as a corepressor of CiR. *J Cell Biol,* 203:575-583

◎ Huang S, Zhang Z, Zhang C, Lv X, Zheng X, Chen Z, Sun L, Wang H, Zhu Y, Zhang J, Yang S, Lu Y, Sun Q, Tao Y, Liu F, **Zhao Y**#, and Chen D#. (2013) Activation of Smurf E3 ligase promoted by Smoothened regulates Hedgehog signaling through targeting Patched turnover. *PLoS Biol*, 11:e1001721

◎ Zhang Y, Fu L, Qi X, Zhang Z, Xia Y, Jia J, Jiang J, **Zhao Y**#, and Wu G#. (2013) Structural insight into the mutual recognition and regulation between Suppressor of Fused and Gli/Ci. *Nat Commun*, 4:2608

◎ Yang X, Mao F, Lv X, Zhang Z, Fu L, Lu Y, Wu W, Zhou Z, Zhang L#, and **Zhao Y**#. (2013) Drosophila Vps36 regulates Smo trafficking in Hedgehog signaling. *J Cell Sci*, 126:4230-4238

◎ Zhang Z, Lv X, Jiang J, Zhang L#, and **Zhao Y**#. (2013) Dual roles of Hh signaling in the regulation of somatic stem cell self-renewal and germline stem cell maintenance in Drosophila testis. *Cell Res*, 23:573-576

◎ Shi D, Lv X, Zhang Z, Yang X, Zhou Z, Zhang L#, and **Zhao Y**#. (2013) Smoothened oligomerization/higher order clustering in lipid rafts is essential for high Hedgehog activity transduction. *J Biol Chem*, 288:12605-12614

◎Shi S, Deng YZ, Zhao JS, Ji XD, Shi J, Feng YX, Li G, Li JJ, Zhu D, Koeffler HP, **Zhao Y**, Xie D. (2012) RACK1 promotes non-small-cell lung cancer tumorigenicity through activating sonic hedgehog signaling pathway. *J Biol Chem*, 287(11):7845-7858

◎ Zhang Y, Mao F, Lu Y, Wu W, Zhang L#, and **Zhao Y**#. (2011) Transduction of the Hedgehog signal through the dimerization of Fused and the nuclear translocation of Cubitus interruptus. *Cell Res*, 21:1436-1451

◎ Chen Y, Li S, Tong C, **Zhao Y**, Wang B, Liu Y, JiaJ, Jiang J. (2010) G protein-coupled receptor kinase 2 promotes high-level Hedgehog signaling by regulating the active state of Smo through kinase-dependent and kinase-independent mechanisms in Drosophila. *Genes Dev*, 24:2054-2067

◎ Jin Y, Xu J, Yin MX, Lu Y, Hu L, Li P, Zhang P, Yuan Z, Ho MS, Ji H, **Zhao Y**#, and Zhang L#. (2013) Brahma is essential for Drosophila intestinal stem cell proliferation and regulated by Hippo signaling. *Elife*, 2:e00999

◎ Guo T, Lu Y, Li P, Yin M, Lv D, Zhang W, Wang H, Zhou Z, Ji H, **Zhao Y**#, and Zhang L#. A novel partner of Scalloped regulates Hippo signaling via antagonizing Scalloped-Yorkie activity. *Cell Res*, 2013, 23:1201-1214

Decoding Ci: from partial degradation to inhibition

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The evolutionarily conserved Hedgehog (Hh) signaling pathway is transduced by the Cubitus interruptus (Ci)/Gli family of transcription factors, which can be degraded either completely or partially from a full-length form (Ci155/GliFL) to a truncated repressor ($Ci75/Gli^{R}$) by proteasomes. The mechanism by which proteasomes distinguish ubiquitinated Ci/Gli to carry out complete versus partial degradation is not known. We show that Ter94/p97 ATPase is involved in processing Ci and Gli3 into Ci75 and $Gli3^{R}$. We demonstrate that Cul1-Slimb-based E3 ligase modifies Ci by efficient addition of K11-linked ubiquitin chains. $Ter94^{Ufd1\text{-}like/dNpl4}$ complex interacts directly with Cul1-Slimb, and, intriguingly, it prefers K11-linked ubiquitinated Ci. Thus, Ter94 ATPase and K11-linked ubiquitination in Ci contribute to the selectivity by proteasomes for partial degradation. In addition, aberrant activation of Hh signaling is associated with various human cancers, but the mechanism through which Ci^{R}/Gli^{R} properly represses target gene expression is poorly understood. We find that Atro directly binds to Ci through its C terminus. The N terminus of Atro interacts with a histone deacetylase, Rpd3, to recruit it to a Ci-binding site at the *decapentaplegic* (*dpp*) locus and reduce *dpp* transcription through histone acetylation regulation. The repressor function of Atro in Hh signaling is dependent on Ci. Furthermore, Rerea, a homologue of Atro in zebrafish, represses the expression of Hh-responsive genes. We propose that the Atro–Rpd3 complex plays a conserved role to function as a Ci^{R} corepressor.

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Recent Selected Publications

◎ Ting CH, Ho PJ, **Yen BL***. (2014) Age-related decreases of serum-response factor (SRF) levels in human MSCs are involved in skeletal muscle differentiation and engraftment capacity. *Stem Cells Dev* doi:10.1089/scd.2013.0231.

◎ **Yen BL**, Yen ML, Hsu PJ, Liu KJ, Wang CH, Bai CH, Sytwu HK (2013) Multipotent mesenchymal stromal cells mediate the expansion of myeloid-derived suppressor cells through the HGF/c-met axis and STAT3. *Stem Cell Reports* 1(2): 139–151.

◎ Yeh YH, **Yen BL**, Hsu SH (2013) Placental stem cells for cartilage tissue engineering. In: *Perinatal Stem Cells*: *Biology & Clinical Applications*, editors Atala A & Murphy SV, Springer, Berlin, Germany, in press.

◎ Ho PJ, Yen ML, Tang BC, Chen CT, **Yen BL** (2013) H2O2 accumulation mediate differentiation capacity alteration but not proliferative decline in senescent human fetal mesenchymal stem cells. *Antioxid Redox Signal* 18;1895-905.

◎ Wang CH, Yen ML, Wu CC, Liou JY, Lee YW, Chou C, Wu KK, Lai YK, **Yen BL** (2013) The role of RhoA kinase inhibition in human placenta-derived multipotent cells on neural phenotype and cell survival. *Biomaterials* 34:3223-30.

◎ Chang TC, Liu CC, Hsing EW, Liang SM, Chi YH, Sung LY, Lin SP, Shen TL, Ko BS, **Yen BL**, Yet SF, Wu KK, Liou JY (2012) 14-3-3σ regulates β-catenin-mediated mouse embryonic stem cell proliferation by sequestering GSK-3β. *PloS One* 7(6):e40193.

◎ Ho PJ, Yen ML, Yet SF, **Yen BL** (2012) Current applications of human pluripotent stem cells: possibilities and challenges (review). *Cell Transplant* 21(5):801-14.

◎ Lin CY, Peng CY, Huang TT, Wu ML, Lai YL, Chen PF, Chen CF, **Yen BL**, Wu KK, Yet SF (2012) Exacerbation of oxidative stress-induced cell death and differentiation in induced pluripotent stem cells lacking heme oxygenase-1. *Stem Cells Dev* 10:1675-87.

◎ Chen PM, Yen ML, Liu KJ, Sytwu HK, **Yen BL*** (2011) Immunomodulatory properties of human adult and fetal multipotent mesenchymal stem cells (review). *J Biomed Sci* 18:49-59.

◎ Huang G, Dai L, **Yen BL**, Hsu SH (2011) Spheroid formation of mesenchymal stem cells on chitosan and chitosan-hyaluronan membranes. *Biomaterials* 32:6929-45.

◎ Hsu SH*, Huang TB, Cheng SJ, Weng SY, Tsai CL, Tseng CS, Chen DC, Liu TY, Fu KY, **Yen BL** (2011) Chondrogenesis from human placenta-derived multipotent cells (PDMCs) in 3D scaffolds for cartilage tissue engineering. *Tissue Eng Part A* 17:1549-60.

◎ Liu KJ, Wang CJ, Chang CJ, Hu HI, Hsu PJ, Wu YC, Bai CH, Sytwu HK, **Yen BL** (2011) Surface expression of HLA-G is involved in mediating immunomodulatory effects of placenta-derived multipotent cells (PDMCs) towards natural killer lymphocytes. *Cell Transplant* 20:1721-30.

◎ Ho PJ, Yen ML, Lin JD, Chen LS, Hu HI, Yeh CK, Lin CY, Peng CY, Yet SF, **Yen BL** (2010) Endogenous KLF4 expression in human fetal endothelial cells allows for reprogramming to pluripotency with just OCT3/4 and SOX2. *Arterioscler Thromb Vasc Biol* 30:1905-7.

Mechanisms involved in human mesenchymal stem cell (MSC) immunomodulation: interactions with innate and adaptive leukocytes

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Despite the isolation of human embryonic stem cells (hESCs) and the more recently discovered induced pluripotent stem cells (iPS), many critical issues still surround these cells in terms of prevalent clinical use, the most important likely being the ethical concerns of hESC derivation, and tumorigenic potential of both these pluripotent stem cells. Increasing reports of plasticity for many adult stem cells (ASCs) have brought excitement and hope for broad therapeutic application, but these are rare cells and controversy still exists regarding ASC transdifferentiation capacity, especially to the extent of being clinically efficacious. Thus, the search continues for ethically conducive, easily accessible, and high-yielding source of stem cells. We have isolated and studied the immunobiology of novel sources of fetal-stage mesenchymal stem cells (MSCs), including placenta-derived multipotent cells (PDMCs) and hESC-derived mesenchymal progenitors. Fetal tissues are developmentally and immunologically more naïve than adult tissue, and often are discarded after the birth of the neonate, making this source ideal for isolation of progenitor cells for therapeutic use. We have found that these fetal-stage MSCs exhibit many markers common to adult bone marrow (BM) MSCs including CD105 and CD73, as well as hESC markers such as SSEA-4. Highly proliferative compared with adult BMMSCs, fetal-stage MSCs possess broader differentiation capacity than adult BMMSCs based on our recent data, and are strongly immunomodulatory towards allogeneic leukocytes. Mechanistically, suppression of allogeneic leukocytes by fetal-stage MSCs is largely due to secreted factors, and can be surprisingly enhanced with interferon-γ, a proinflammatory cytokine. The immunomodulation of fetal-stage MSCs extend to both innate and adaptive leukocytes, via mechanisms which we are interested in delineating for more efficacious clinical application of these versatile stem cells. With such broad immunosuppressive properties and multilineage differentiation capacity, fetal-stage MSCs may represent a potential cell source for therapeutic use.

Session V

Stem Cell Research in Cancer

Moderator:

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Recent Selected Publications

◎ Yin J, Yi Y, Fu X, and **Hu P**. (2012) Forkhead transcription factors control stem cell fate determination.*Chinese Journal of Cell Biology,* 34(12): 1197-1206.

◎ Xu C, Lv X, Chen Z, He Z, Li G, Ma Y, Hui L, Xie B, Gao Y, Ding X, Hu Y, **Hu P***, Han JDJ*, and Wang X. (2012) Genome-wide roles of Foxa2 in directing liver specification. *J Mol Cell Biol* 4(6), 420-422.

◎ Yao J, Fetter RD, **Hu P**, Betzig E, Tjian R. (2011) Sub-Nuclear Spatial Segregation of Genes and Core Promoter Selectivity Factors. *Genes and Development* 25(6):569-80..

◎ **Hu P**, Geles KG, Paik JH, DePinho RA, and Tjian R. (2008) Co-dependent Activators Direct Myoblast Specific MyoD Transcription. *Developmental Cell* 15(4): 534-546.

◎ Deato MDE, Marr MT, Sottero T, Inouye C, **Hu P***, and Tjian R. (2008) MyoD targets TAF3/TRF3 to activate myogenin transcription. *Molecular cell*, 32(1):96-105.

◎ Gao X^, Tate P^, **Hu P**, Tjian R , Skarnes WC, and Wang Z. (2008) ES cell pluripotency and germ-layer formation require the SWI/SNF chromatin remodeling component BAF250a. *Proceedings of the National Academy of Science*s 105(18): 6656-6661. (^these authors contribute equally to the paper.)

◎ **Hu P** and Hernandez N (2006) RNA polymerase III transcription, in Genome KNOWLEDGEBASE.（http://www.genomeknowledge.org/referring2GK.html.） Cold Spring Harbor Press.

◎ **Hu P**, Wu S, Hernandez N. (2004) A role for beta-actin in RNA polymerase III transcription *Genes Dev*. 18(24):3010-5.

◎ **Hu P**, Samudre K, Wu S, Sun Y, and Hernandez N. (2004) CK2 phosphorylation of Bdp1 executes cell cycle-specific RNA polymerase III transcription repression. *Mol Cell.* 16(1):81-92.

◎ **Hu P**, Wu S, and Hernandez N. (2003) A Minimal RNA Polymerase III Transcription System from Human Cells Reveals Positive and Negative Regulatory Roles for CK2. *Mol. Cell*, 12(3):699-709.

◎ **Hu P**, Wu S, Sun Y, Yuan CC, Kobayashi R, Myers MP, and Hernandez N. (2002) Characterization of Human RNA Polymerase III Identifies Orthologues for Saccharomyces cerevisiae RNA Polymerase III Subunits. *Mol. Cell. Biol*. 22: 8044-8055.

◎ Chong SS, **Hu P**, and Hernandez N. (2001) Reconstitution of Transcription from the Human U6 Small Nuclear RNA Promoter with Eight Recombinant Polypeptides and a Partially Purified RNA polymerase III complex. *J. Biol. Chem.* 276: 20727 - 20734.

◎ **Hu P**, An C and Chen Z. (1999) Prokaryotic Expressed Trichosanthin and Other Two Proteins have Anti-fungal Activity in vitro. *Acta Microbiologica Sinica.* Vol. 39, No. 3: 234-240.

◎ Gu H, Qu L, **Hu P**, Chen Z. (2006). Modern Biotechnology. Advanced Education Press. ISBN: 9787040121902

◎ Gu H, Qu L, **Hu P**, Chen Z. (1998) Introduction to Modern Biotechnology. Springer Press. ISBN:7040065711

Activation of Wnt signaling prevents muscle atrophy

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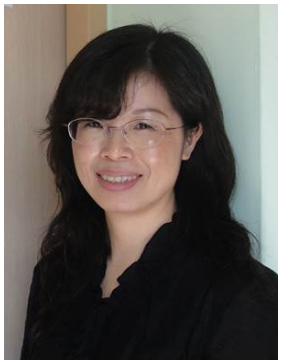
Muscle is the most important organ for movements and metabolism. Maintenance of muscle mass in highly critical to keep muscle functions. Muscle atrophy is the most common pandemia in aged population. There is no efficacious medicine to prevent or treat muscle atrophy thus far. Therefore, the elucidation of the mechanism on muscle atrophy will shed light on developing medicines to prevent or treat muscle atrophy.

We found that Wnt signaling activities have changed dramatically upon muscle differentiation. Differentiated muscle fibers maintain significantly higher Wnt signaling levels compared to other organs. The increased Wnt signaling levels were achieved via decreased expression of of Wnt inhibitor Dickkopf3 (Dkk3). Inhibition of Wnt signaling in terminal differentiated muscle cells by DKK3 overexpression or small molecule inhibitors resulted in muscle atrophy. Further studies showed that Wnt signaling level could affect the binding profile of β-catenin on its target genes, thus resulting in selective activation of atrophy related genes.



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Recent Selected Publications

◎ Chang TS, Wu YC, Su WC, Chi CC, Chang PJ, Lee KF, Liu JJ, Tung SY, Kuo LM, Ho HN, Ling TY, and **Huang YH***. (2014) Activation of IL6/IGF-IR confers poor prognosis of HBV-related hepatocellular carcinoma through induction of OCT4/NANOG expression. *Clin Cancer Res.*

◎ **Huang YH**, Lin MH, Wang PC, Wu YC, Chiang HL, Wang YL, Chang JH, Huang YK, Gu SY, Ho HN, Ling TY. (2014) Hypoxia inducible factor 2α/insulin-like growth factor receptor signal loop supports the proliferation and Oct-4 maintenance of mouse germline stem cells. *Mol Human Reprod.* In Press.

◎ Wu YC, Ling TY, Lu SH, Kuo HC, Ho HN, Yeh SD, Shen CN, **Huang YH*** (2012) Chemotherapeutic Sensitivity of Testicular Germ Cell Tumors Under Hypoxic Conditions Is Negatively Regulated by SENP1-Controlled Sumoylation of OCT4. *Cancer Res.* 72(19):4963-73.

◎ Chuang CY, Lin KI, Hsiao M, Lee S, Chen HF, **Huang YH**, Lin SP, Ho HN, Kuo HC (2012) Meiotic competent human germ cell-like cells derived from human embryonic stem cells induced by BMP4/WNT3A signaling and OCT4/EpCAM selection. *J Biol Chem.* 287(18):14389-401.

◎ Liao CJ, **Huang YH**, Au HK, Wang LM, Chu ST (2012) The cancer marker neutrophil gelatinase-associated lipocalin is highly expressed in human endometrial hyperplasia. *Mol Biol Rep.* 39(2):1029-36.

◎ Lee SY, Huang GW, Shiung JN, **Huang YH**, Jeng JH, Kuo TF, Yang JC, Yang WC (2012) Magnetic cryopreservation for dental pulp stem cells. *Cells Tissues Organs.* 196(1):23-33.

◎ Chen CH, Yeh YC, Wu GJ, **Huang YH**, Lai WF, Liu JY, Tzeng CR (2010) Tracking the rejection and survival of mouse ovarian iso- and allografts in vivo with bioluminescent imaging. *Reproduction.* 140(1):105-12.

◎ **Huang YH**, Yang JC, Wang CW, Lee SY (2010) Dental stem cells and tooth banking for regenerative medicine. *J Exp Clin Med*. 2(3):111-117.

◎ Yang RB, Au HK, Tzeng CR, Tsai MT, Wu P, Wu YC, Ling TY, **Huang YH*** (2010) Characterization of a novel cell-surface protein expressed on human sperm. *Hum Reprod.*, 25(1):42-51.

◎ **Huang YH***, Chin CC, Ho HN, Chou CK, Shen CN, Kuo HC, Wu TJ, Wu YC, Hung YC, Chang CC, Ling TY (2009) Pluripotency of mouse spermatogonial stem cells maintained by IGF-1-dependent pathway. *FASEB J.* 23(7):2076-2087.

◎ **Huang YH**, Lee TH, Chan KJ, Hsu FL, Wu YC, Lee MH (2008) Anemonin is a natural bioactive compound that can regulate tyrosinase-related proteins and mRNA in human melanocytes. *J Dermatol Sci.* 49(2):115-123.

◎ Cheng CJ, Wu YC, Shu JA, Ling TY, Kuo HC, Wu JY, Chang EE, Chang SC, **Huang YH*** (2007) Aberrant expression and distribution of the OCT-4 transcription factor in seminomas. J Biomed Sci 14(6):797-80.

Niche regulation of stemness expression in cancer

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The expression of pluripotency-related genes in cells is linked to drug susceptibility which challenges the current therapy. Niche environment plays a critical role in stemness expression in cells either of embryonic or somatic stage. In somatic cancers, hepatocellular carcinoma (HCC) is an inflammation-associated cancer which is commonly associated with chronic hepatitis B virus (HBV) infection. We found the expression of pluripotency-related genes is regulated by IL-6-induced IGF/IGF-IR activation in HBV-HCC, and is associated with tumor aggressiveness and recurrence. In a large cohort of frozen HCC samples, we found significant correlation between IGF-IR and OCT4/NANOG transcriptional expressions and this association is preferentially found in hepatitis B virus (HBV)-related HCC (HBV-HCC) than those in non-HBV-HCC. Consistently, immunohistochemical staining showed significant positive correlation between the expressions of the OCT4/NANOG and the phosphorylation of IGF-IR in HCC tumor tissues. And, the stemness expression was significantly associated with tumor aggressiveness and poor disease-free survival (DFS). Niche IL-6 stimulated the expression of autocrine IGF-I and IGF-IR in a STAT-dependent manner, which stimulated the stemness-related properties in both the cell lines and the xenograft mouse tumors. The inhibition of the IGF-IR activation by RNA interference and molecular inhibitor significantly suppressed the IL-6-induced stemness-related properties in vitro and in vivo, suggesting that the IL-6-induced IGF-IR-mediated signaling is a potential target for individualized adjuvant therapy against HBV-HCC.

In embryonic stage, niche hypoxia down-regulated the OCT4 level and results in chemoresistance and poor prognosis in human pluripotent testicular germ cell tumors (TGCTs). Hypoxia reduces OCT4 levels and increases the resistance of embryonal carcinoma (EC) cells to cisplatin and bleomycin by regulating the SUMO1 peptidase SENP1. Overexpression of SENP1 reduced the Su-OCT4 level induced by SUMO1gg overexpression, thereby maintaining OCT4 levels and enhancing chemosensitivity. Mechanistic investigations revealed that OCT4 sumoylation occurred at K123, as overexpression of an OCT4-K123R mutant effectively reduced the level of Su-OCT4 under hypoxic conditions. These results demonstrated that hypoxia reduces OCT4 expression levels in pluripotent germ cell tumors to increase drug resistance, and these effects could be countered to ablate the suppressive effects of hypoxia on chemosensitivity.

Session VI

Translational Medicine in Cancer

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Recent Selected Publications (selected from 384 peer-reviewed publications)

◎ Shen J, Xia W, Khotskaya YB, Huo L, Nakanishi K, Lim SO, Du Y, Wang Y, Chang WC, Chen CH, Hsu JL, Wu Y, Lam YC, James BP, Liu X, Liu CG, Patel DJ, **Hung MC** (2013) EGFR modulates miRNA maturation in response to hypoxia through phosphorylation of Ago 2. *Nature* 497(7449):383-387.

◎ Huang TH, Huo LF, Wang YN, Xia W, Wei Y, Chang SS, Chang WC, Fang YF, Chen CT, Lang JY, Tu C, Wang Y, Hsu MC, Kuo HP, Ko HW, Shen J, Lee HH, Lee PC, Wu Y, Chen CH, **Hung MC** (2013) EGFR potentiates MCM7-mediated DNA replication through tyrosine phosphorylation of Lyn kinase in human cancers. *Cancer Cell* 23(6):796-810.

◎ Wang Y, Ding QQ, Yen CJ, Xia W, Izzo JG, Lang JY, Li CW, Miller SA, Wang X, Lee DF, Hsu JL, Hsu JM, Huo LF, LaBaff AM, Liu DP, Huang TH, Lai CC, Tsai FJ, Chang WC, Chen CH, Wu TT, Buttar NS, Wang KK, Wu Y, Wang H, Ajani J, **Hung MC** (2012) The crosstalk of mTOR/S6K1 and Hedgehog pathways. *Cancer Cell* 21: 374–387.

◎ Chang CJ, Chao CH, Xia W, Yang JY, Xiong Y, Li CW, Yu WH, Rehman SK, Hsu J, Lee HH, Liu M, Chen CT, Yu D, **Hung MC** (2011) p53 regulates epithelial-mesenchymal transition (EMT) and stem cell properties through modulation of miRNAs. *Nature Cell Biology* 13(3):317-323.

◎ Chang CJ, Yang JY, Xia W, Chen CT, Xie X, Chao CH, Woodward WA, Hortobagyi GN, **Hung MC** (2011) EZH2 promotes expansion of breast cancer tumor initiating cells through activation of RAF-β-catenin signaling. *Cancer Cell* 19 (1):86-100.

◎ Wei Y, Chen YH, Li LY, Lang J, Yeh SP, Shi B, Yang CC, Yang JY, Lin CY, Lai CC, **Hung MC** (2011) CDK1-dependent phosphorylation of EZH2 suppresses methylation of H3K27 and promotes osteogenic differentiation of human mesenchymal stem cell. *Nat Cell Biol* 13 (1):87-94.

◎ Lang JY, Hsu JL, Meric-Bernstam F, Chang CJ, Wang Q, Bao Y, Yamaguchi H, Xie X, Woodward WA, Yu D, Hortobagyi GN, **Hung MC** (2011) BikDD eliminates breast cancer initiating cells and synergizes with lapatinib for breast cancer treatment. *Cancer Cell* 20(3):341-356.

◎ Lee, D-F., Kuo, H-P., Liu, M., Chou, C-K., Xia, W., Du, Y., Shen, J., Shen, J., Chen, C-T., Huo, L., Hsu, M-C., Li, C-W., Ding, Q., Liao, T-L., Lai, C-C., Lin, A-C. Chang, Y-H, Tsai, S-F., Li, L-Y. and **Hung, M-C** (2009) KEAP1 E3 ligase-mediated down regulation of NF-κB signaling by targeting IKKβ. *Mol Cell* 36: 131-140.

◎ Yang, J-Y., Zong, C.S., Xia, W., Yamaguchi, H., Ding, Q., Xie, X., Lang, J-Y., Lai, C-C., Chang, C-J., Huang, W-C., Huang, H., Kuo, H-P., Lee, D-F., Li, L-Y., Lien H-C., Cheng, X, Chang, K-J., Hsiao, C-D., Tsai, F-J., Tsai, C-H., Sahin, AA., Muller, WJ., Mills, GB., Yu, D., Hortobagyi, GN. and **Hung, M-C** (2008) Erk promotes tumorigenesis by inhibiting Foxo3a via MDM2-mediated degradation. *Nature Cell Biology.* 10:138-148.

◎ Lee, D-F., Kuo, H-P., Chen, C-T., Hsu, J-M., Sun, H-L., Chou, C-K., Wei, Y., Li, L-Y.,Ping, B., Huang, W-C., He, X., Hung, J-Y., Lai, C-C., Ding, Q., Su, J-L., Yang, J-Y., Sahin, A.A., Hortobagyi, G.N., Tsai, F-J., Tsai, C-H. and **Hung, M-C**. (2007) Suppression of TSC1 by IKKβ confers tumor angiogenesis through the mTOR pathway. *Cell.* 130:440-455.

Novel signaling pathways in cancer cells and development of targeted therapy

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We discovered a non-canonical pathway of Hedgehog (Hh) through mTOR in addition to established, or canonical, pathway for activating Gli1 that both pathways converge to Gli1 leading to esophagus cancer. Crosstalk between these two pathways is a challenge, but our experiments showed a combination of the mTOR inhibitor RAD-001 (Everolimus®) and the Hedgehog inhibitor GDC-0449 (Erivedge®) steeply reduced the tumor burden in a mouse model of esophageal adenocarcinoma. GDC-0449, approved in January 2012 by the FDA for treatment of metastatic basal cell carcinoma, however, but in other cancers, such as ovarian and pancreas are resistant to GDC-0449. Our finding serve as a guidance for clinical trials of the combination for esophageal and other cancers including breast, ovarian and pancreatic cancers that could be directed by the antibody for phosphorylated Gli1 and the presence of plain Gli1, which would indicate a need to use both drugs (***Cancer Cell*** 21, 374–387, 2012).

Previously, we have developed a targeted approach by developing a pancreatic cancer-specific expression vector (C-VISA) to treating pancreatic cancer with effective therapeutic efficacy and safety in noninvasive imaging models. Targeted expression of BikDD, a potent proapoptotic gene driven by C-VISA, exhibited significant antitumor effects on pancreatic cancer and prolonged survival in multiple xenograft and syngeneic orthotopic mouse models of pancreatic tumors with virtually no toxicity (***Cancer Cell*** 12:52-65, 2007). A phase I IND protocol has been approved by the FDA in October 2010. A phase I clinical trial for advance pancreatic cancer patients will be initiated in 2012. Recently, we developed a breast cancer specific expression vector can specifically target breast cancer cells but not normal cells. Our study also presents a new strategy for killing breast cancer stem cells and for increasing their susceptibility to other therapies, thus lowering the chance of chemoresistance and recurrence (***Cancer Cell*** 20:341-356, 2011). Cancer stem cells are a major culprit for drug resistance and recurrence. This study has important clinical implication and has been selected in the Leading Edge of Targeted Therapeutics in the Oct 14, 2011 issue of ***Cell***.

In addition, we have recently identified an interesting mechanism showing how EGFR regulates DNA synthesis and repair through phosphorylation of histone H4. We have also identified a EGFR arginine methylation as a marker to predict resistance to cetuximab.

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Recent Selected Publications

◎ Jiao S, Wang H, Shi Z, Dong A, Zhang W, Song X, He F, Wang Y, Zhang Z, Wang W, Wang X, Guo T, Li P, Zhao Y, Ji H, Zhang L, **Zhou Z** (2014) Gastric Cancer Therapy by a Peptide Mimicking VGLL4 Function as a YAP Antagonist. *Cancer Cell*. 25: 166-180.

◎ Zhang W, Gao Y, Li P, Shi Z, Guo T, Li F, Han XK, Feng Y, Zheng C, Wang Z, Chen H, **Zhou Z***, Zhang L* and Ji H*. (2014) Identification of VGLL4 as a new tumor suppressor in lung cancer negatively regulating the YAP-TEADs transcriptional complex. *Cell Research.* doi:10.1038/cr.2014.10

◎ Zhang Z, Feng J, Pan C, Lv X, Wu W, **Zhou Z**, Liu F, Zhang L, and Zhao Y. (2013) Atrophin-Rpd3 complex represses Hedgehog signaling by acting as a corepressor of CiR. *Journal of Cell Biology.* 203: 575-583

◎ Guo T, Lu Y, Li P, Yin M, Lv D, Zhang W, Wang H, **Zhou Z**, Ji H, Zhao Y and Zhang L. (2013) A novel partner of Scalloped regulates Hippo signaling via antagonizing Scalloped-Yorkie activity. *Cell Research.* 23:1201-1214

◎ Huang H, Wang S, Yin M, Dong L, Wang C, Wu W, Lu Y, Feng M, Dai C, Guo X, Li L, Zhao B, **Zhou Z**, Ji H, Jiang J, Zhao Y, Liu X, Zhang L. (2013) Par-1 Regulates Tissue Growth by Influencing Hippo Phosphorylation Status and Hippo-Salvador Association. *PLoS Biol.* 11(8):e1001620.

◎ Zhang M, Dong L, Shi Z, Jiao S, Zhang Z, Zhang W, Liu G, Chen C, Feng M, Hao Q, Wang W, Yin M, Zhao Y, Zhang L, **Zhou Z.** (2013) Structural mechanism of CCM3 heterodimerization with GCKIII kinases. *Structure.* 21:680-688.

◎ Shi Z, Jiao S, Zhang Z, Ma M, Zhang Z, Chen C, Wang K, Wang H, Zhang L, Zhao Y, **Zhou Z.** (2013) Structure of the MST4 in complex with MO25 provides insights into its activation mechanism. *Structure*. 21:449-561.

◎ Wang W, Shi Z, Jiao S, Chen C, Wang H, Liu G, Wang Q, Zhao Y, Greene MI, **Zhou Z.** (2012) Structural insights into SUN-KASH complexes across the nuclear envelope. *Cell Research.* 22:1440-1452.

◎ Song X, Li B, Xiao Y, Chen C, Wang Q, Liu Y, Berezov A, Xu C, Gao Y, Wu SL, Zhang H, Karger B, Hancock W, Wells A, **Zhou Z***, Greene M*. (2012) Structural and biological features of FOXP3 dimerization relevant to regulatory T cell function. *Cell Reports.* 1:665-675

Development of a peptide-based YAP inhibitor sheds new light on gastric cancer treatment

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The Hippo pathway has been implicated in suppressing tissue overgrowth and tumor formation by restricting the oncogenic activity of YAP. As an emerging significant player in tumorigenesis, the Hippo pathway has attracted increasing attention for the development of new anti-cancer drugs. In contrast to targeting upstream regulators such as MST1/2 and LATS, inhibition of YAP, the ultimate downstream effector of Hippo signaling, may provide a more effective and direct way to redress the Hippo pathway. However, transcriptional regulators that inhibit YAP activity have not been well studied. Here, we uncover clinical importance for VGLL4 in gastric cancer suppression and find that VGLL4 directly competes with YAP for binding TEADs. Importantly, VGLL4's tandem Tondu domains are not only essential but also sufficient for its inhibitory activity towards YAP. Our findings that VGLL4 is a natural antagonist of YAP and its TDU region is sufficient for YAP inhibition allowed for the development of a peptide-based YAP inhibitor. This peptide mimicking VGLL4 function potently suppresses gastric tumor growth in vitro and in vivo, providing an opportunity for treating gastric cancer which currently lacks effective treatment options. Collectively, our study indicates that disruption of YAP-TEADs interaction by a VGLL4-mimicking peptide may be a promising therapeutic strategy against YAP-driven human cancers.

Session VI

Translational Medicine in Cancer

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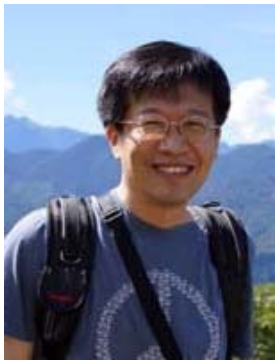

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Recent Selected Publications

◎ Lee, H. Y.; Tsai, A. C.; Chen, M. C.; Shen, P. J.; Cheng, Y. C.; Kuo, C. C.; Pan, S. L.; Liu, Y. M.; Liu, J. F.; Yeh, T. K.; Wang, J. C.; Chang, C. Y.; Chang, J. Y.*; **Liou, J. P.*** (2014) Azaindolylsulfonamides, with a More Selective Inhibitory Effect on Histone Deacetylase 6 Activity, Exhibit Antitumor Activity in Colorectal Cancer HCT116 Cells. *J. Med. Chem. in press*.

◎ Chang, C. Y.; Chuang, H. Y.; Lee, H. Y.; Yeh, T. K.; Kuo, C. C.; Chang, C. Y.; Chang, J. Y.*; **Liou, J. P.*** (2014) Antimitotic and vascular disrupting agents: 2–Hydroxy-3,4,5-trimethoxybenzophenones. *Eur. J. Med. Chem. 77*, 306-314.

◎ Chen, C.H.; Chen, M. C.; Wang, J. C.; Tsai, A. C.; Chen, C. S.; **Liou, J. P.***; Pan, S. L. *; Teng, C. M.* (2014) Synergistic interaction between the HDAC inhibitor, MPT0E028, and sorafenib in liver cancer cells *in vitro* and *in vivo. Clin. Cancer Res. 20*, 1274-1287.

◎ Liu YM, Chen HL, Lee HY, **Liou JP** (2014) Tubulin inhibitors: a patent review. *Expert Opin Ther Pat.* 24 (1):69-88.

◎ Lee HY, Yang CR, Lai MJ, Huang HL, Hsieh YL, Liu YM, Yeh TK, Li YH, Mehndiratta S, Teng CM, **Liou JP.** (2013) 1-Arylsulfonyl-5-(N-hydroxyacrylamide)indolines Histone Deacetylase Inhibitors Are Potent Cytokine Release Suppressors. *ChemBioChem* 14:1500-1504.

◎ Lee HY, Pan SL, Su MC, Liu YM, Kuo CC, Chang YT, Wu JS, Nien CY, Mehndiratta S, Chang CY, Wu SY, Lai MJ, Chang JY, **Liou JP** (2013) Furanylazaindoles: Potent Anticancer Agents in Vitro and in Vivo. *Journal of Medicinal Chemistry* 56:8008-8018.

◎ Lai MJ, Huang HL, Pan SL, Liu YM, Lee HY, Yeh TK, Huang PH, Teng CM, Chen CS, Chuang HY, **Liou JP.** (2012) Synthesis and Biological Evaluation of 1-Arylsulfonyl-5-(N-hydroxyacrylamide)indoles as Potent Histone Deacetylase Inhibitors with Antitumor Activity in vivo. *J. Med. Chem.* 55:3777-3791.

◎ Lee HY, Lee LW, Nien CY, Kuo CC, Lin PY, Chang CY, Chang JY, **Liou JP** (2012) Application of Suzuki arylation, Sonogashira ethynylation and Rosenmund–von Braun cyanation in the exploration of substitution effects on the anticancer activity of 2-aroylquinolines. *Organic & Biomolecular Chemistry* 10:9593-9600.

◎ Huang HL, Lee HY, Tsai AC, Peng CY, Lai MJ, Wang, JC, Pan SL, Teng CM, **Liou, JP** (2012) Anticancer Activity of MPT0E028, a Novel Potent Histone Deacetylase Inhibitor, in Human Colorectal Cancer HCT116 Cells In Vitro and In Vivo. *PLOS ONE* 7:e43645.

◎ **Liou JP**, Chang JY (2012) ARYL SUBSTITUTED SULFONAMIDE COMPOUNDS AND THEIR USE AS ANTICANCER AGENTS US patent.

◎ Hsieh CC, Lee HY, Nien CY, Kuo CC, Chang CY, Chang JY, **Liou JP** (2011) Synthesis and Biological Evaluation of 4-Aroyl-6,7,8-Trimethoxyquinolines as a Novel Class of Anticancer. *Agents Molecules* 16:2274-2284.

◎ Chuang HY, Chang JY, Lai MJ, Kuo CC, Lee HY, Hsieh HP, Chen YJ, Chen LT, Pan WY, **Liou JP** (2011) 2-Amino-3,4,5-Trimethoxybenzophenones as Potent Tubulin Polymerization Inhibitors. *ChemMedChem* 6:450-456.

Azaindolyl compounds with more selective inhibitory effect on histone deacetylase 6 activity, exhibit antitumor activity in colorectal cancer HCT116 cells

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A series of indolylsulfonylcinnamic hydroxamates has been synthesized.**MPT0B291**, which has a 7-azaindole core cap, was shown to have antiproliferative activity against KB, H460, PC3, HSC-3, HONE-1, A549, MCF-7, TSGH, MKN45, HT29, and HCT116 human cancer cell lines. Pharmacological studies indicated that **MPT0B291** functions as a potent HDAC inhibitor with an IC_{50} value of 0.1 μM. It is highly selective for histone deacetylase 6 (HDAC6) and is 60-fold more active than against HDAC1, 223-fold more active than against HDAC2. It has a good pharmacokinetic profile with oral bioavailability of 33%. In *in vivo* efficacy evaluations in colorectal HCT116 xenografts, **MPT0B291** suppresses tumor growth more effectively than SAHA and is therefore seen as a suitable candidate for further investigation

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Recent Selected Publications

◎ Tsai YC, Yeh CH, Tzen KY, Ho PY, Tuan TF, Pu YS, **Cheng AL**, Cheng JC (2013) Targeting epidermal growth factor receptor/human epidermal growth factor receptor 2 signalling pathway by a dual receptor tyrosine kinase inhibitor afatinib for radiosensitisation in murine bladder carcinoma. *Eur J Cancer* 49(6):1458-66.

◎ Chen KF, Chen HL, Shiau CW, Liu CY, Chu PY, Tai WT, Ichikawa K, Chen PJ, **Cheng AL** (2013) Sorafenib and its derivative SC-49 sensitize hepatocellular carcinoma cells to CS-1008, a humanized anti-DR5 antibody. *Br J Pharmacol.* 168(3):658-72.

◎ Shao YY, Lu LC, Lin ZZ, Hsu C, Shen YC, Hsu CH, **Cheng AL** (2012) Prognosis of advanced hepatocellular carcinoma patients enrolled in clinical trials can be classified by current staging systems. *Br J Cancer* 107,10, pp1672-1677.

◎ Shao YY, Chen CL, Ho MC, Huang CC, Tu HC, Hsu CH, **Cheng AL** (2012) Dissimilar Immunohistochemical Expression of ERK and AKT between Paired Biopsy and Hepatectomy Tissues of Hepatocellular Carcinoma. *Anticancer Res.* 32,11,pp4865-4870.

◎ Jou SY, Chang CC, Wu CH, Chen MR, Tsai CH, Chuang WH, Chen YH, **Cheng AL**, Doong SL (2012) BCL10GFP fusion protein as a substrate for analysis of determinants required for Mucosa-Associated Lymphoid Tissue 1 (MALT1)-mediated cleavage. *J Biomed Sci.* 19,1, pp85.

◎ Chen KH, Chou YH, **Cheng AL** (2012) Primary Squamous Cell Carcinoma of the Thyroid With Cardiac Metastases and Right Ventricle Outflow Tract Obstruction. *J Clin Oncol.* 30,26,ppe260-e263.

◎ Chen KF, Lin JP, Shiau CW, Tai WT, Liu CY, Yu HC, Chen PJ, **Cheng AL** (2012) Inhibition of Bcl-2 improves effect of LCL161, a SMAC mimetic, in hepatocellular carcinoma cells. *Biochem Pharmacol.* 84,3,pp268-277.

◎ Shao YY, Huang CC, Lin SD, Hsu CH, **Cheng AL** (2012) Serum Insulin-Like Growth Factor-1 Levels Predict Outcomes of Patients with Advanced Hepatocellular Carcinoma Receiving Antiangiogenic Therapy. *Clin Cancer Res.*18,14,pp3992-3997.

◎ Lin CH, Chen YC, Chiang CJ, Lu YS, Kuo KT, Huang CS, Cheng WF, Lai MS, You SL, **Cheng AL** (2012) The emerging epidemic of estrogen-related cancers in young women in a developing Asian country. *Int J Cancer.*130,11,pp2629-2637.

◎ Lu YS, Chou CH, Tzen KY, Gao M, **Cheng AL**, Kulp SK, Cheng JC (2012) Radiosensitizing effect of a phenylbutyrate-derived histone deacetylase inhibitor in hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys.* 83,2,ppe181-e189.

◎ Kuo SH, Yeh KH, Wu MS, Lin CW, Hsu PN, Wang HP, Chen LT, **Cheng AL** (2012) Hpylori eradication therapy is effective in the treatment of early-stage H. pylori-positive gastric diffuse large B-cell lymphomas. *Blood*.119,21,pp4838-4844.

Microorganism and cancer: a revisit of the spectrum of *H. Pylori*-related gastric lymphoma

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Low-grade mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach (gastric MALT lymphoma) is associated with *Helicobacter pylori* infection. The eradication of *H. pylori* using antibiotics is successful in 60% to 80% of affected patients. In contrast to the previous paradigm, we and other investigators have shown that a certain proportion of patients with *H. pylori*-positive early-stage diffuse large B-cell lymphoma (DLBCL) of the stomach with histological evidence of MALT lymphoma (high-grade transformed gastric MALT lymphoma, gastric DLBCL[MALT]) achieved long-term complete pathological remission (pCR) after first-line *H. pylori* eradication therapy (HPE), indicating that the loss of *H. pylori* dependence and high-grade transformation are separate events in the progression of gastric lymphoma. In addition, patients with *H. pylori*-positive gastric DLBCL without histological evidence of MALT (gastric pure DLBCL) may also respond to HPE. A long-term follow-up study showed that patients who achieved pCR remained lymphoma-free. Gastric MALT lymphoma is indirectly influenced by *H. pylori* infection through T-cell stimulation, and recent studies have shown that *H. pylori*-triggering chemokines and their receptors, *H. pylori*-associated epigenetic changes, *H. pylori*-regulated microRNA expression, and tumor infiltration by $CD4^+CD25^+$ regulatory T cells contribute to lymphomagenesis of gastric MALT lymphoma. Recent studies have also demonstrated that the translocation of CagA into B lymphocytes inhibits apoptosis through p53 accumulation, BAD phosphorylation, and the upregulation of Bcl-2 and Bcl-X_L expression. In gastric MALT lymphoma, CagA may stimulate lymphomagenesis directly through the regulation of signal transduction, and intracellular CagA is associated with *H. pylori* dependence. These findings represent a substantial paradigm shift, compared with the classical theory of *H. pylori*-reactive T cells contributing indirectly to the development of MALT lymphoma. In conclusion, a wide range of *H. pylori*-related gastric lymphomas have been identified. The use of antibiotics as the sole first-line therapy for early-stage gastric pure DLBCL requires validation in a prospective study. The clinical and biological significance of the CagA oncoprotein in the lymphomagenesis of gastric MALT lymphoma warrants further study.

Poster Abstracts

103 年度第 11 屆海峽兩岸生物醫學獎摘要

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Education

2009.9-present Ph.D. candidate, Shanghai Institute of Biochemistry and Cell Biology, CAS

2005.9-2009.7 B.S., Huazhong Agricultural University

Major Activities

Oral presentation: Regulation of miRNA processing by a multifunctional protein YB-1. Cold Spring Harbor Asia Conferences-RNA Biology, Suzhou, 2012.

Honors and Awards

2013 Merit student, Chinese Academy of Sciences

Research Interests

miRNA biogenesis

Regulation of miRNA processing by a multifunctional protein YB-1

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MicroRNAs (miRNAs) are small non-coding RNAs that are key regulators of diverse cellular processes. Most miRNAs are generated from primary transcripts through two consecutive cleavage steps involving two RNase III enzymes: Drosha and Dicer. MiRNA maturation can be regulated at each individual step. However, the molecular mechanisms that regulate miRNA processing are largely unknown. The Y box-binding protein 1 (YB-1) is a member of the evolutionarily conserved nucleic acid binding protein family, which exhibits multiple functions in transcription, alternative splicing, mRNA stability, mRNA localization, and translation. YB-1 is overexpressed in many malignant tissues, and considered as a marker of tumorigenesis. Previously we characterized the CAUC sequence as an YB-1 binding motif with high affinity through a SELEX approach. Using iCLIP assay, we found that YB-1 also has a strong preference to bind CAUC motifs *in vivo*. We showed that specific binding of YB-1 to the terminal loop of miRNAs containing the CAUC motif influences the miRNA biogenesis. Overexpression of YB-1 in cultured cells inhibited the maturation of the miRNA. Using *in vitro* processing assays, we demonstrate that YB-1 interferes with the cleavages by Drosha and Dicer, respectively. Further analyses indicate that YB-1 blocks the accessibility of microprocessor and Dicer to the miRNA. Our study may provide a new mechanism for understanding the role of YB-1 in tumorigenesis.

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EDUCATION:

1999-2003: B.S in Veterinary Medicine, College of Veterinary Medicine,
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2004-2007: M.S in Veterinary Medicine, College of Veterinary Medicine,
Nanjing Agricultural University
2009-2013: Ph. D. in cellular biology, Shanghai Institute of Biochemistry and Cell Biology, CAS

HONOURS:

2012: The National Scholarship of China
2012: All around good Student of Chinese Academy of Science
2007: Outstanding thesis award of Jiangsu province of China
2002: Excellent Student Leaders of Inner Mongolia University for the Nationalities
2002: Professional third-class scholarship of Inner Mongolia University for the Nationalities
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MAJOR RESEARCH INTERESTS:

My major research interests are lung cancer plasticity and it's functional correlation with drug resistance. With the integration of genomic studies of human lung cancer samples and functional biological studies using human cell lines and animal models, we plan to gain an insightful understanding of lung cancer biology and related mechanism, which potentially helps the development of better therapeutics in clinic. We have recently proven for the first time that mouse lung adenocarcinoma with Lkb1 deficiency could transit to squamous cell carcinoma via the mixed pathology as intermediate. We will continue to work on this project and translate our findings in animal models to human clinical samples.

BIBLIOGRAPHY:

1 Han X, Li F, Fang Z, Gao Y, Li F, Fang R, Yao S, Sun Y, Li L, Zhang W, Ma H, Xiao, Q,

Ge G, Fang J, Wang H, Zhang L, Wong K, Chen H, Hou Y, Ji H. Transdifferentiation of Lung Adenocarcinoma with Lkb1 Deficiency to Squamous Cell Carcinoma in Mice. Nat Commun, 2014, doi:10.1038/ncomms4261.

2 Zhang W, Gao Y, Li P, Shi Z, Guo T, Li F, Han X, Feng Y, Zheng C, Wang Z, Li F, Chen H, Zhou Z, Zhang L, Ji H. VGLL4 functions as a new tumor suppressor in lung cancer by negatively regulating the YAP-TEAD transcriptional complex. Cell Res, 2014, doi: 10.1038/cr.2014.10.

3 Fang R, Zheng C, Sun Y, Han X, Gao B, Li C, Liu H, Wong KK, Liu X, Chen H, Ji H. Integrative genomic analysis reveals a high frequency of LKB1 genetic alteration in Chinese lung adenocarcinomas, J Thorac Oncol, (2013, in press).

4 Li F, Feng Y, Fang R, Fang Z, Xia J, Han X, Liu X, Chen H, Liu H & Ji H. Identification of RET gene fusion by exon array analyses in "pan-negative" lung cancer from never smokers. Cell Res, 22, 928-931, (2012).

5 Li C, Sun Y, Fang R, Han X, Luo X, Wang R, Pan Y, Hu H, Zhang Y, Pao W, Shen L, Ji H & Chen H. Lung adenocarcinomas with HER2-activating mutations are associated with distinct clinical features and HER2/EGFR copy number gains. J Thorac Oncol,7, 85-89, (2012).

6 Li C, Sun Y, Fang Z, Han X, Fang R, Zhang Y, Pan Y, Zhang W, Ren Y, Ji H & Chen H. Comprehensive analysis of epidermal growth factor receptor gene status in lung adenocarcinoma. J Thorac Oncol, 6, 1016-1021, (2011).

7 Li C, Fang R, Sun Y, Han X, Li F & Gao Y, et al., Spectrum of oncogenic driver mutations in lung adenocarcinomas from East Asian never smokers. PLoS One, 6, e28204, doi:10.1371/journal.pone. (2011).

8 Sun Y, Fang R, Gao B, Han X, Zhang J, J H & Pao W, et al., Comparable rate of EGFR kinase domain mutation in lung adenocarcinomas from Chinese male and female never-smokers. Acta Pharmacol Sin, 31, 647-648,(2010).

9 Sun Y, Ren Y, Fang Z, Li C, Fang R, Gao B, Han X, Tian W, Pao W, Chen H & Ji H. Lung adenocarcinoma from East Asian never-smokers is a disease largely defined by targetable oncogenic mutant kinases. J Clin Oncol, 28, 4616-4620,(2010).

10 Gao Y, Xiao Q, Ma H, Li L, Liu J, Feng Y, Fang Z, Wu J, Han X, Zhang J, Sun Y, Wu G, Padera R, Chen H, Wong KK, Ge G & Ji H. LKB1 inhibits lung cancer progression through lysyl oxidase and extracellular matrix remodeling. Proc Natl Acad Sci U S A, 107, 18892-18897, (2010).

11 Gao B, Sun Y, Zhang J, Ren Y, Fang R, Han X & Shen L, et al., Spectrum of LKB1, EGFR, and KRAS mutations in chinese lung adenocarcinomas. J Thorac Oncol, 5, 1130-1135, (2010).

12 Zhang L, Han X, Qi Y, Liu Y & Chen Q. Seasonal effects on apoptosis and proliferation of germ cells in the testes of the Chinese soft-shelled turtle, Pelodiscus sinensis. Theriogenology, 69, 1148-1158, (2008).

13 Han X, Zhang L, Li M, Bao H, Hei N & Chen Q. Seasonal changes of sperm storage and correlative structures in male and female soft-shelled turtles, Trionyx sinensis. Anim Reprod Sci, 108, 435-445, (2008).

14 Han X, Zhang L, Li M, Bao H, Hei N & Chen Q. Ultrastructure of anterior uterus of the oviduct and the stored sperm in female soft-shelled turtle, Trionyx sinensis. Anat Rec, (Hoboken) 291, 335-351, (2008).

15 Zhang L, Han X, Li M, Bao H& Chen Q. Spermiogenesis in soft-shelled turtle, Pelodiscus sinensis. Anat Rec, (Hoboken) 290, (2007).

Transdifferentiation of lung adenocarcinoma with *Lkb1* deficiency to squamous cell carcinoma in mice

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Lineage transition in adenocarcinoma (ADC) and squamous cell carcinoma (SCC) of non-small cell lung cancer (NSCLC), as implicated by clinical observation of mixed ADC and SCC pathologies in adenosquamous cell carcinoma (Ad-SCC), remains a fundamental yet unsolved question. Here we provide *in vivo* evidences showing the transdifferentiation of lung cancer from ADC to SCC in mice: *Lkb1*-deficient lung ADC progressively transdifferentiates into SCC, via pathologically mixed mAd-SCC as intermediate. We find that reduction of lysyl oxidase (Lox) in *Lkb1*-deficient lung ADC decreases collagen disposition and triggers extracellular matrix remodeling and eventually up-regulates *p63* expression, a SCC lineage survival oncogene. Pharmacological Lox inhibition promotes the transdifferentiation, whereas ectopic Lox expression significantly inhibits this process. Notably, ADC and SCC show differential responses to Lox inhibition. Collectively, our findings have discovered the *de novo* transdifferentiation of lung ADC to SCC in mice and provided mechanistic insight that may have important implications for lung cancer treatment.

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學習工作背景 ：

2010 年 9 月—至今: 中科院上海生物化學與細胞生物學研究所，碩博連讀

2005 年 9 月—2009 年 7 月： 山東大學生物工程系，生物制藥專業，學士

研究領域：

2010 年 9 月進入中國科學院上海生命科學研究所進行細胞生物學及發育生物學的研究，集神經與 Hedgehog 信號途徑在果蠅小腸幹細胞中的作用的研究。

Hh signaling in neurons controls intestinal stem cell fate in *Drosophila*

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Shanghai Institute of Biochemistry and Cell Biology, CAS

Homeostasis of intestine is maintained by intestinal stem cells (ISCs) and their progenies, responding to various injuries. A complex autonomic nervous system spreads over intestine, however, whether and how neurons regulate intestine homeostasis is largely unknown. Here, we demonstrate that neurons contribute to the control of *Drosophila* intestinal homeostasis, and Hedgehog (Hh) signaling activity in neurons is essential for the determination of ISCs' fate. Downregulation of Hh signaling in neurons promotes ISCs' proliferation and inhibits their differentiation to enterocytes (ECs) while upregulation of Hh signaling in neurons promotes this differentiation process. Furthermore, Hh is secreted by enterocytes (ECs), offering a feedback signal to ISCs niche. Collectively, neuronal Hh signaling is essential for the determination of ISCs' fate.

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Educational History:

2008-2012 Shandong University School of Lifescience

2012-present Shanghai Institute of Biochemistry and Cell Biology

Research Interest:

Mechanisms and dynamics of TNF induced apoptosis

Mathematic modeling of IKK signaling network

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The IκB kinase complex (IKK) is a key regulator of immune responses, inflammation, cell survival, and tumorigenesis. Recent studies revealed that IKK inhibits TNFα-induced apoptosis through two distinct but cooperative mechanisms: activation of NF-κB signaling pathway and inactivation of the proapoptotic BH-3 only protein BAD. Here, we established a mathematic model to study the underling mechanism of IKK signaling. Using this model, we found that IKK signaling network obeys feedforward loop regulation mechanism. Both activation of NF-κB and inactivation of BAD are necessary but not sufficient for IKK to suppress TNFα-induced apoptosis. Feedforward loop regulation mechanism also ensures the robustness and reversibility for IKK signaling network in prevention of TNFα-induced catastrophe.

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Education and Training

2004.9-2008.7 B.S.in Biological technology, Oceanography Institute, Shandong University

2008.9-now M.S. & Ph.D. Shanghai Institute of Biochemistry and Cell Biology, CAS

Research Experience

2011-now Applications ProTA to identify mechanisms of drug action of Bortezomib and Carfilzomib, to identify mechanisms of HBV infection

2009-2011 Methodological and technical development for high-throughput ProTA (Protein Turnover Assay)

2008-2009 Construction of the yeast genetic operation（The yeast two hybrid；gene knockout et al）

Invited Presentation

2013.05.18 The Eleventh National colloquium on the enzymatic, Wuxi. ***"ProTA(Protein Turnover Assay):Profiling human protein degradome to identify mechanisms of drug action and resistance"***

Techniques

Recombinant DNA and genome engineering; Flow cytometry; Bioinformatics analysis for omic data; yeast and bacteria genetic operation (The yeast two hybrid;gene knockout; gene knockin et al); high-throughput experimentation; protein expression.

List of Publications

◎ **Tao Yu**, Yonghui Tao, Tao Zhang, Zi Chen, Meiqiang Yang, Peng Chen, Kangcheng Ruan, Yan Zhang, Ronggui Hu, Profiling human protein degradome delineates cellular responses to proteasomal inhibition and reveals a feedback mechanism in regulating proteasome homeostasis**,** Cell Research, 2014, in press.

◎ Xingxing Xu, Yonghui Tao, Xing Fu, Kan Chen, **Tao Yu**, Xiaoyan Ding, Kangcheng Ruan, Naihe Jing, Ronggui Hu, ZIP-seq: Genome-wide Mapping of Trinucleotide Repeats at Single Base Resolution, Journal of Molecular Cell Biology,2013, in press.

Profiling human protein degradome delineates cellular responses to proteasomal inhibition and reveals a feedback mechanism in regulating proteasome homeostasis

Tao Yu (于濤), Yonghui Tao, Tao Zhang, Zi Chen, Meiqiang Yang, Peng Chen, Yan Zhang, Kangcheng Ruan and Ronggui Hu*

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Global change in protein turnover (protein degradome) constitutes a central part of cellular responses to intrinsic or extrinsic stimuli. However, profiling protein degradome remains technically challenging. Recently, inhibition of proteasome, e.g. using Bortezomib (BTZ), has emerged as a major chemotherapeutic strategy for treating multiple myeloma and other human malignancies, but systematic understanding of the mechanisms for BTZ drug action and tumor resistance is yet to be achieved. Here we developed and applied a dual-fluorescence-based Protein Turnover Assay (ProTA) to quantitatively profile global changes in human protein degradome upon BTZ treatment. ProTA and subsequent network analyses delineates potential molecular basis for BTZ action and tumor drug resistance in BTZ chemotherapy. Finally, combined use of BTZ with drugs targeting the ProTA-identified key genes or pathways in BTZ action has overcome BTZ-resistance in multiple myeloma cells. Remarkably, BTZ stabilizes proteasome subunit (*PSMC1*) and proteasome assembly factor (*PSMD10*), suggesting a previously unappreciated mechanism for regulating proteasome homeostasis. Therefore, ProTA is emerging as a novel tool for profiling human protein degradome to elucidate potential mechanisms of drug action and resistance, which might facilitate therapeutic development targeting proteostasis to treat human disorders.

103 年度第 11 屆優秀論文獎摘要

優秀論文獎編號: PhD1

Dual role for Islet-1 in promoting striatonigral and repressing striatopallidal genetic programs to specify striatonigral identity

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Striatal projection neurons comprise two populations of striatonigral and striatopallidal neurons. These two neuronal populations play distinct roles in controlling movement-related functions in the basal ganglia circuits. An important issue is how striatal progenitors are developmentally specified into these two distinct neuronal populations. In the present study, we characterized the function of Isl1, a LIM-homeodomain transcription factor, in striatal development. Genetic fate mapping showed that Isl1+ progeny specifically developed into a subpopulation of striatonigral neurons that transiently expressed Isl1. In *Nestin-Cre;Isl1f/f* knockout mouse brain, differentiation of striatonigral neurons was defective as evidenced by decreased expression of striatonigral-enriched genes. Striatonigral axonal projections were also impaired and abnormal apoptosis was observed in *Isl1* knockout striatum. It was of particular interest that striatopallidal-enriched genes were concomitantly up-regulated in *Isl1* mutant striatum, suggesting de-repression of striatopallidal genes in striatonigral neurons in the absence of Isl1. The suppression of striatopallidal genes by *Isl1* was further examined by over-expression of Isl1 in the striatum of *Drd2-EGFP* transgenic mice using *in utero* electroporation. Ectopic Isl1 expression was sufficient to repress Drd2-EGFP signals in striatopallidal neurons. Our study suggests that Isl1 specifies the cell fate of striatonigral neurons not only by orchestrating survival, differentiation and axonal projections of striatonigral neurons, but also by suppressing striatopallidal-enriched genes. The dual action of developmental control by *Isl1* in promoting appropriate striatonigral but repressing inappropriate striatopallidal genetic profiles may ensure sharpening the striatonigral identity during development.

優秀論文獎編號: PhD2

Suberoylanilide hydroxamic acid (SAHA) causes tumor growth slowdown and triggers autophagy in glioblastoma stem cells

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Chiung-Chyi Shen and Jiunn-Liang Ko
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Although suberoylanilide hydroxamic acid (SAHA), a histone deacetylase inhibitor, has been used in clinical trials for cancer therapies, its pharmacological effects occur through a poorly understood mechanism. Here, we report that SAHA specifically triggers autophagy and reduces cell viability via promotion of apoptosis in the late phase of glioblastoma stem cells (GSC s). Using a cell line cultured from a glioblastoma biopsy, we investigated the properties and effects of GSC s under SAHA treatment in vitro. In vivo xenograft assays revealed that SAHA effectively caused tumor growth slowdown and the induction of autophagy. SAHA was sufficient to increase formation of intracellular acidic vesicle organelles, recruitment of LC3-II to the autophagosomes, potentiation of BEC N1 protein levels and reduced SQSTM1 levels. We determined that SAHA triggered autophagy through the downregulation of AKT-MTOR signaling, a major suppressive cascade of autophagy. Interestingly, upon depletion or pharmacological inhibition of autophagy, SAHA facilitates apoptosis and results in cell death at the early phase, suggesting that SAHA -induced autophagy functions probably act as a prosurvival mechanism. Furthermore, our results also indicated that the inhibition of SAHA –induced autophagy using chloroquine has synergistic effects that further increase apoptosis. Moreover, we found that a reduced dose of SAHA functioned as a potent modulator of differentiation and senescence. Taken together, our results provide a new perspective on the treatment of GSC s, indicating that SAHA is a promising agent for targeting GSC s through the induction of autophagy.

優秀論文獎編號: PhD3

Hexamethonium reverses the lethal cardiopulmonary damages in a rat model of brainstem lesions mimicking fatal Enterovirus 71 encephalitis

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Wen-Yu Ho, Chi-Cheng Lai, Jyh-Seng Wang, Luo-Ping Ger,
Michael Hsiao and Ching-Jiunn Tseng
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OBJECTIVES: Among enterovirus 71 infections, brainstem encephalitis progressing abruptly to cardiac dysfunction and pulmonary edema causes rapid death within several hours. However, no currently known early indicators and treatments can monitor or prevent the unexpectedly fulminant course. We investigate the possible mechanisms and treatment of fatal enterovirus 71 infections to prevent the abrupt progression to cardiac dysfunction and pulmonary edema by using an animal model.

DESIGN: Treatment study.
SETTING: Research laboratory.
SUBJECTS: Sprague-Dawley rats.

INTERVENTIONS: We microinjected 6-hydroxydopamine or vitamin C into nucleus tractus solitarii of the rat and evaluated the cardiopulmonary changes after treatment with ganglionic blocker.

MEASUREMENTS AND MAIN RESULTS: The time course of changes in the heart and lungs of rats with brainstem lesions were investigated. Rats were administered 6-hydroxydopamine to induce brainstem lesions, causing acute hypertension in 10 minutes and acute elevations of catecholamines accompanied by acute cardiac dysfunction and increased strong expressions of connexin 43 gap junction protein in heart and lung specimens by immunohistochemical staining within 3 hours. Severe pulmonary hemorrhagic edema was produced within 6 hours, and the rats expired rapidly within 7 hours. After hexamethonium treatment, it was found that the acute hypertension induced by 6-hydroxydopamine lesions was immediately reversed and the acute high rise of catecholamine serum level was significantly attenuated within 3 hours, accompanied by preserved cardiac output and decreased expressions of connexin 43 in the heart and lungs. No pulmonary edema occurred and the rats survived for more than 14 hours.

CONCLUSIONS: Early hexamethonium treatment attenuates acute excessive release of catecholamines to prevent cardiac dysfunction and pulmonary edema for increasing survival rate.

優秀論文獎編號: PhD4

Recombinant protein rVP1 upregulates BECN1-independent autophagy, MAPK1/3 phosphorylation and MMP9 activity via WIPI1/WIPI2 to promote macrophage migration

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The monocyte/macrophage is critical for regulating immune and antitumor responses. Recombinant capsid protein VP1 (rVP1) of foot-and-mouth disease virus induces apoptosis and inhibits migration/metastasis of cancer cells. Here, we explored the effects of rVP1 on macrophages. Our results showed that rVP1 increased LC3-related autophagosome formation via WIPI1 and WIPI2 in a BECN1-independent manner. rVP1 treatment increased macrophage migration that was attenuated by knockdown of ATG5, ATG7, WIPI1 or WIPI2 and was abolished when both WIPI1 and WIPI2 were depleted. Treatment of macrophages with rVP1 increased matrix metalloproteinase-9 (MMP9) activity and phosphorylated mitogen-activated protein kinase 1/3 (MAPK1/3), two major mediators of cell migration. Knockdown of WIPI1, WIPI2, ATG5 and ATG7 but not BECN1 attenuated the rVP1-mediated increase in MAPK1/3 phosphorylation and MMP9 activity. These results indicated that rVP1 upregulated autophagy, MAPK1/3 phosphorylation and MMP9 activity to promote macrophage migration, which was dependent on WIPI1, WIPI2, ATG5 and ATG7 but not BECN1.

優秀論文獎編號: PhD5

CTGF increases drug resistance to paclitaxel by upregulating survivin expression in human osteosarcoma cells

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Osteosarcoma is the most common primary malignant tumor, and its treatments require more effective therapeutic approaches. Paclitaxel has a broad range of antitumor activities, including apoptosis-inducing effects. However, the majority of tumors in patients with advanced cancer eventually develop chemoresistance. Connective tissue growth factor (CTGF) is a secreted protein that modulates the invasiveness of certain human cancer cells by binding to integrins. However, the effect of CTGF in paclitaxel-mediated chemotherapy is unknown. Here, we report that the expression of CTGF in osteosarcoma patients was significantly higher than CTGF expression in normal bone tissues. Overexpression of CTGF increased the resistance to paclitaxel-mediated cell apoptosis. In contrast, knockdown of CTGF expression by CTGF shRNA increased the chemotherapeutic effect of paclitaxel. In addition, CTGF increased resistance to paclitaxel-induced apoptosis through upregulation of survivin expression. Moreover, the AMP-activated protein kinase (AMPK)-dependent nuclear factor kappa B (NF-κB) pathway mediated paclitaxel-increased chemoresistance and survivin expression. In a mouse xenograft model, overexpression of CTGF promoted resistance to paclitaxel. In contrast, knockdown of CTGF expression increased the therapeutic effect of paclitaxel in this model. In conclusion, our data indicate that CTGF might be a critical oncogene of human osteosarcoma involved in resistance to paclitaxel treatment.

優秀論文獎編號: PhD6

Cytotoxicity, oxidative stress, apoptosis and the autophagic effects of silver nanoparticles in mouse embryonic fibroblasts

Yu-Hsuan Lee (李宥萱), Fong-Yu Cheng, Hui-Wen Chiu, Jui-Chen Tsai, Chun-Yong Fang, Chun-Wan Chen and Ying-Jan Wang

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With the advancement of nanotechnology, nanomaterials have been comprehensively applied in our modern society. However, the hazardous impacts of nanoscale particles on organisms have not yet been thoroughly clarified. Currently, there exist numerous approaches to perform toxicity tests, but common and reasonable bio-indicators for toxicity evaluations are lacking. In this study, we investigated the effects of silver nanoparticles (AgNPs) on NIH 3T3 cells to explore the potential application of these nanoparticles in consumer products. Our results demonstrated that AgNPs were taken up by NIH 3T3 cells and localized within the intracellular endosomal compartments. Exposure to AgNPs is a potential source of oxidative stress, which leads to the induction of reactive oxygen species (ROS), the upregulation of Heme oxygenase 1 (HO-1) expression, apoptosis and autophagy. Interestingly, AgNPs induced morphological and biochemical markers of autophagy in NIH 3T3 cells and induced autophagosome formation, as evidenced by transmission electron microscopic analysis, the formation of microtubule-associated protein-1 light chain-3 (LC3) puncta and the expression of LC3-II protein. Thus, autophagy activation may be a key player in the cellular response against nano-toxicity.

優秀論文獎編號: PhD7

Optogenetic control of selective neural activity in multiple freely moving Drosophila adults

Ming-Chin Wu*, Li-An Chu*, **Po-Yen Hsiao (蕭伯彥)***, Yen-Yin Lin, Chen-Chieh Chia, Tsung-Ho Liua, Chien-Chung Fu, and Ann-Shyn Chiang

(* M.-C.W., L.-A.C., and P.-Y.H. contributed equally to this work)

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We present an automated laser tracking and optogenetic manipulation system (ALTOMS) for studying social memory in fruit flies (Drosophila melanogaster). ALTOMS comprises an intelligent central control module for high-speed fly behavior analysis and feedback laser scanning (~40 frames per second) for targeting two lasers (a 473-nm blue laser and a 593.5-nm yellow laser) independently on any specified body parts of two freely moving Drosophila adults. By using ALTOMS to monitor and compute the locations, orientations, wing postures, and relative distance between two flies in real time and using high-intensity laser irradiation as an aversive stimulus, this laser tracking system can be used for an operant conditioning assay in which a courting male quickly learns and forms a long-lasting memory to stay away from a freely moving virgin female. With the equipped lasers, channelrhodopsin-2 and/or halorhodopsin expressed in selected neurons can be triggered on the basis of interactive behaviors between two flies. Given its capacity for optogenetic manipulation to transiently and independently activate/inactivate selective neurons, ALTOMS offers opportunities to systematically map brain circuits that orchestrate specific Drosophila behaviors.

優秀論文獎編號: PhD8

Enhancement of ADP release from the RAD51 presynaptic filament by the SWI5-SFR1 complex

Guan-Chin Su (蘇綸勤) , Chan-I Chung, Chia-Yu Liao, Sheng-Wei Lin, Cheng-Ting Tsai, Tao Huang, Hung-Wen Li and Peter Chi

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Homologous recombination catalyzed by the RAD51 recombinase eliminates deleterious DNA lesions from the genome. In the presence of ATP, RAD51 forms a nucleoprotein filament on single-stranded DNA, termed the presynaptic filament, to initiate homologous recombination-mediated DNA doublestrand break repair. The SWI5-SFR1 complex stabilizes the presynaptic filament and enhances its ability to mediate the homologous DNA pairing reaction. Here we characterize the RAD51 presynaptic filament stabilization function of the SWI5-SFR1 complex using optical tweezers. Biochemical experiments reveal that SWI5-SFR1 enhances ATP hydrolysis by single-stranded DNA-bound RAD51. Importantly, we show that SWI5-SFR1 acts by facilitating the release of ADP from the presynaptic filament. Our results thus provide mechanistic understanding of the function of SWI5-SFR1 in RAD51-mediated DNA recombination.

優秀論文獎編號: PhD9

Histone demethylase retinoblastoma binding protein-2 promotes lung tumorigenesis and cancer metastasis

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The retinoblastoma binding protein-2 (RBP2), a demethylase capable of removing the di- or tri-methyl group from lysine 4 of histone 3, promotes gastric cancer cell growth and is enriched in drug-tolerant lung cancer cells. The gene knockout study further suggests that RBP2 loss suppresses tumor initiation in mice lacking the tumor suppressor Rb or MEN1. Nevertheless, the direct link of RBP2 to tumorigenesis and the underlying mechanism are unclear. Here we attack the question by exploring the role of RBP2 in lung cancer. We show that RBP2 was overexpressed in human lung cancer tissues and that RBP2 depletion impaired lung cancer cell proliferation, motility, migration, invasion and metastasis. Mechanistically, the oncogenic potential of RBP2 depended on its demethylase and DNA contact activities. Moreover, RBP2 upregulated the expressions of cyclins D1 and E1, while suppressed the expression of cyclin-dependent kinase inhibitor p27, likely contributing to RBP2-mediated lung cancer cell proliferation. Microarray analysis further revealed that RBP2 promoted the expression of integrin beta 1 (ITGB1), a membrane receptor involved in cancer metastasis through cell adhesion and recognition. RBP2 directly bound to p27, cyclin D1, and ITGB1 promoters and the exogenous cyclin D1, cyclin E1 or ITGB1 expression rescued cell proliferation and migration/invasion, respectively, reduced by RBP2 knockdown. Taken together, these results not only demonstrate a positive role of RBP2 in lung tumorigenesis and metastasis, but also uncover novel RBP2 targets for the oncogenic function of RBP2. Targeting RBP2 may provide a useful therapeutic strategy in lung cancer treatment.

優秀論文獎編號: PhD10

Chromosome 19 open reading frame 80 is upregulated by the thyroid hormone and modulates autophagy and lipid metabolism

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The thyroid hormone, T_3, regulates cell growth, differentiation and development through binding to the nuclear thyroid hormone receptor (THR), a member of the steroid/THR superfamily of ligand-dependent transcriptional factors. T_3 modulates lipid metabolism in liver, although the detailed molecular mechanisms are unclear at present. Here, by a microarray analysis we identified a novel *chromosome 19 open reading frame 80* (*C19orf80*) which was activated by T_3. T_3 stimulation led to upregulation of both mRNA and protein levels of *C19orf80*. Immunofluorescence analysis revealed a vesicle-like pattern of C19orf80 around lipid droplets or within the lysosome-associated compartment in cells. Furthermore, T_3 treatment as well as C19orf80 overexpression specifically activated the autophagic response and lipid metabolism, as observed from lipidated LC3 (LC3-II) and levels of oxygen consumption rate, respectively. Reciprocally, knockdown of C19orf80 obstructed T_3-activated autophagy and lipolysis. Moreover, treatment with autolysosome maturation inhibitors, ammonium chloride and chloroquine, not only suppressed the T_3-activated autophagic process but also lipid metabolism. Our results collectively suggest that T_3 regulates lipid metabolism through a C19orf80-activated autophagic process.

優秀論文獎編號: PhD11

Instructive nanofiber scaffolds with VEGF create a microenvironment for arteriogenesis and cardiac repair

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The promyelocytic leukaemia (PML) protein controls multiple tumour suppressive functions and is downregulated in diverse types of human cancers through incompletely characterized post-translational mechanisms. Here we identify USP11 as a PML regulator by RNAi screening. USP11 deubiquitinates and stabilizes PML, thereby counteracting the functions of PML ubiquitin ligases RNF4 and the KLHL20–Cul3 (Cullin 3)–Roc1 complex. We find that USP11 is transcriptionally repressed through a Notch/Hey1-dependent mechanism, leading to PML destabilization. In human glioma, Hey1 upregulation correlates with USP11 and PML downregulation and with high-grade malignancy. The Notch/Hey1-induced downregulation of USP11 and PML not only confers multiple malignant characteristics of aggressive glioma, including proliferation, invasiveness and tumour growth in an orthotopic mouse model, but also potentiates self-renewal, tumour-forming capacity and therapeutic resistance of patient-derived glioma-initiating cells. Our study uncovers a PML degradation mechanism through Notch/Hey1-induced repression of the PML deubiquitinase USP11 and suggests an important role for this pathway in brain tumour pathogenesis.

優秀論文獎編號: PhD12

Spontaneous seroclearance of Hepatitis B seromarkers and subsequent risk of hepatocellular carcinoma

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Background and Aims: The associations between long-term risk of hepatocellular carcinoma (HCC) and spontaneous seroclearance of hepatitis B virus (HBV) e antigen (HBeAg), HBV DNA, and HBV surface antigen (HBsAg) have never been examined by a prospective study using serially measured seromarkers. This study aimed to assess the importance of spontaneous HBeAg, HBV DNA, and HBsAg seroclearance in the prediction of HCC risk.

Methods: This study included 2,946 HBsAg seropositive individuals who were seronegative for antibodies against hepatitis C virus and free of liver cirrhosis. Serial serum samples collected at study entry and follow-up health examinations were tested for HBeAg, HBV DNA and HBsAg. Cox proportional hazards models were used to calculate the hazard ratios of developing HCC after seroclearance of HBV markers.

Results: The hazard ratio (95% confidence interval) of developing HCC after seroclearance of HBeAg, HBV DNA and HBsAg during follow-up was 0.63 (0.38-1.05), 0.24 (0.11-0.57), and 0.18 (0.09-0.38), respectively, after adjustment for age, gender and serum level of alanine aminotransferase at study entry. High HBV DNA levels at the seroclearance of HBeAg (mean ± standard deviation, 4.35 ± 1.64 log10 IU/mL) may explain the non-significant association between HBeAg seroclearance and HCC risk. Among HBeAg-seronegative participants with detectable serum HBV DNA at study entry, the lifetime (30-75 years old) cumulative incidence of HCC was 4.0%, 6.6% and 14.2%, respectively, for those with seroclearance of both HBV DNA and HBsAg, seroclearance of HBV DNA only, and seroclearance of neither.

Conclusions: Spontaneous seroclearance of HBV DNA and HBsAg are important predictors of reduced HCC risk.

優秀論文獎編號: PhD13

The role of LMBRD1 in regulating cardiac insulin signaling

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Energy homeostasis is crucial in maintaining normal biological functions of cells. Disturbances in such balance often lead to various diseases. Limb region 1 (LMBR1) domain containing 1 gene (*lmbrd1*) encodes a nine-transmembrane LMBD1 protein. Previous study demonstrated that double allele frameshift mutation of *lmbrd1* is associated with lysosomal cobalamin export deficiency, suggesting the participation of LMBD1 in the export of cobalamin from lysosome to the cyotsol. In this study, we have distinguished that heterozygous deletion of *lmbrd1* is sufficient for causing cardiac diseases through a pathway independent of the vitamin B12 metabolic defect. *lmbrd1* ubiquitous heterozygous knockout *lmbrd1*$^{+/-}$ mice exhibited increase in myocardial glucose uptake and insulin receptor signaling that were insensitive to the administration of additional insulin. Consistent with the constitutively activated insulin receptor signaling, *lmbrd1*$^{+/-}$ mice exhibited an increase in heart rate and cardiac muscle contractility, leading to the development of compensated pathological hypertrophy and fibrosis. As *lmbrd1*$^{+/-}$ mice aged, the decrease in ejection fraction and fraction shortening showed signs of ventricular function deterioration. Additional studies using primary ventricular cells demonstrated that knockdown of *lmbrd1* resulted in an elevated signaling of insulin receptor (IR) and its downstream molecule Akt. Confocal and live total internal reflection fluorescence microscopy showed that LMBD1 colocalized and co-internalized with clathrin and IR upon insulin induction. Mutagenesis and phenotypic rescue studies further identified the motifs responsible for assisting the endocytosis of IR. Altogether, LMBD1 plays a regulatory role in the plasma membrane as an adaptor protein for insulin receptor endocytosis and modulates the IR metabolic signaling pathway.

優秀論文獎編號: PhD14

SUMOylated CPAP is required for IKK-mediated NF-κβ activation and enhances HBx-induced NF-κβ signaling in HCC.

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Background & Aims: Constitutive activation of NF-κB is an important event involved in chronic inflammation in hepatocellular carcinoma (HCC). CPAP, which plays important roles in centrosomal functions, was previously identified as the transcriptional co-activator of NF-κB. However, the molecular mechanism is unclear. The goal of this study was to investigate the role of CPAP in activating the NF-κB pathway in HCC.

Methods: SK-Hep1, HuH7, HepG2, HepG2X, Hep3B, and Hep3BX cells with CPAP overexpression or *CPAP* siRNA were used to evaluate activation of NF-κB under TNF-α stimulation by reporter assay, RT-PCR, Q-PCR, and Western blot analysis. *In vivo* SUMO modification of CPAP was demonstrated by an *in situ* PLA assay. Human HCC tissues were used to perform Q-PCR, Western blot, and IHC.

Results: *CPAP* siRNA abolished the interaction between IKKβ and NF-κB, whereas overexpression of CPAP enhanced this interaction and finally led to augmented NF-κB activation by increasing the phosphorylation of NF-κB. CPAP could enter nuclei by associating with NF-κB. Furthermore, CPAP was SUMO-1 modified upon TNF-α stimulus, and this is essential for its NF-κB co-activator activity. SUMO-1-deficient CPAP mutant lost its NF−κB coactivator activity and failed to enter nuclei. Importantly, SUMOylated CPAP could synergistically increase the HBx-induced NF-κB activity.

Conclusions: CPAP is essential for the recruitment of the IKK complex to inactivated NF-κB upon TNF-α treatment. Expression of CPAP was positively correlated with a poor prognosis in HBV-HCC. CPAP has the potential to serve as a therapeutic target for inflammation and inflammation-related diseases.

優秀論文獎編號: PhD15

The contribution of mitochondrial thymidylate synthesis in preventing the nuclear genome stress

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In quiescent fibroblasts, the expression levels of cytosolic enzymes for thymidine triphosphate (dTTP) synthesis are down-regulated, causing a marked reduction in the dTTP pool. In this study, we provide evidence that mitochondrial thymidylate synthesis via thymidine kinase 2 (TK2) is a limiting factor for the repair of ultraviolet (UV) damage in the nuclear compartment in quiescent fibroblasts. We found that TK2 deficiency causes secondary DNA double-strand breaks formation in the nuclear genome of quiescent cells at the late stage of recovery from UV damage. Despite slower repair of quiescent fibroblast deficient in TK2, DNA damage signals eventually disappeared, and these cells were capable of re-entering the S phase after serum stimulation. However, these cells displayed severe genome stress as revealed by the dramatic increase in 53BP1 nuclear body in the G1 phase of the successive cell cycle. Here, we conclude that mitochondrial thymidylate synthesis via TK2 plays a role in facilitating the quality repair of UV damage for the maintenance of genome integrity in the cells that are temporarily arrested in the quiescent state.

優秀論文獎編號: PhD16

The tyrosine kinase Syk differentially regulates Toll-like receptor signaling downstream of the adaptor molecules TRAF6 and TRAF3

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Toll-like receptors (TLRs) are a major family of pattern-recognition receptors and they play a crucial role in innate immunity. Several reports have suggested that spleen tyrosine kinase (Syk) mediates signaling by TLRs; however, the mechanisms involved are unclear. We found that Syk was not only involved in the endocytosis of TLR4, but that it also played a dual role in TLR4-mediated signaling. Stimulation of TLR4 by its ligand lipopolysaccharide (LPS) led to the enhanced activation in Syk-deficient macrophages of the kinase TAK1, which is required for proinflammatory cytokine production, compared to that in wild-type macrophages. In contrast, Syk-deficient macrophages exhibited decreased TLR4-dependent activation of the TBK1-IRF3 pathway, which is required for the production of type I interferons. These two arms of TLR4 signaling, the proinflammatory TAK1-dependent pathway and the immunmodulatory TBK1-dependent pathway, are downstream of complexes containing the E3 ubiquitin ligases TRAF6 and TRAF3, respectively. We found that Syk was present in both TRAF6- and TRAF3-containing signaling complexes; however, the LPS-dependent, lysine-63–linked ubiquitination of TRAF6 and TRAF3 was oppositely regulated by Syk. We also identified the domains of Syk that interacted with TRAF3, TRAF6, TAK1, and TBK1, thus suggesting the role of Syk as a common regulator of various TLR responses. Together, our results demonstrate the opposing regulatory roles of Syk in TLR4-mediated TRAF6 and TRAF3 signaling pathways, which leads us to suggest that Syk may fine-tune the innate immune response to lessen inflammation.

Furthermore, we demonstrate that although Syk negatively controls LPS-induced pro-IL-1β expression, it is a positive regulator of NLRP3 inflammasome activation. Taken together, our results demonstrate the opposite regulatory roles of Syk in TLR4-mediated TRAF6 and TRAF3 signaling pathways, as well as in IL-1β production through pro-IL-1β gene expression and NLRP3 inflammasome activation.

優秀論文獎編號: PhD17

A negative feedback of the HIF-1α pathway via interferon-stimulated gene 15 and ISGylation

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Because cancer has become the highest mortality among diseases, researchers around the world are committed to uncover the potential tumorigenic mechanisms and related intervention of concurring cancer. In recent years, inflammation has regarded as the enhancing characteristics of cancer hallmarks and been proven to contribute to tumor initiation and progression. Inflammation, like hypoxia microenvironment, is also a critical factor for a variety of diseases such as heart disease, stroke and diabetes. Here, we have investigated interactions between microenvironments and relation with cancer development. We found that ISG15 (interferon-stimulated gene 15) modulates hypoxia-inducible factor-1α (HIF-1α) functions. ISG15 conjugation (ISGylation) and ubiquitylation systems play critical roles in hypoxic inflammation. Interferon and hypoxia-mimetic desferoxamine were used to induce ISG15 and HIF-1α expression respectively and to study effects of ISG15 on the HIF-1α activity. We observed free-form HIF-1α is regulated by interferon, and expression of ISG15 is lower in the hypoxic state. Further mechanistic investigation reveals HIF-1α not only physically interacts with ISG15 but also is a substrate for ISGylation at multiple sites. Overexpression of ISG15 disrupted HIF-1α/HIF1β dimerization and subsequently HIF-1α-induced gene expression and tumor growth in xenograft mouse models were attenuated by ISG15 and ISGylation expression. Based on the above results, we concluded and proposed a novel negative feedback mechanism of hypoxia where ISG15 regulates HIF-1α via ISGylation.

優秀論文獎編號: PhD18

Repression of miR-126 and up-regulation of ADM in the stromal endothelium confers angiogenesis of cervical cancer.

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miR-126 is an endothelial-specific microRNA essential for maintaining vessel integrity during development. Its role of tumor angiogenesis in cancer stroma is unclear. This study investigated the temporal and spatial expression and the role of miR-126 in the course of cervical carcinogenesis. miR-126 was found to be mainly expressed in the stromal endothelium of the uterine cervix. This downregulation was recapitulated in a cell coculture model, wherein cross talk of cervical cancer cells and fibroblasts induced a downregulation of miR-126 in human umbilical vein endothelial cells, with consequent increase of tube formation. Coinjection of cancer-associated fibroblasts of human cervix enhanced tumorigenesis of cervical cancer cells, with an increase of microvessel density and dye retention in the tumor vasculature. In association with angiogenesis, host-originated miR-126 in these xenograft tumors was progressively downregulated, whereas supplement of the miR-126 precursor in the coinjection suppressed angiogenesis and tumor growth. A proangiogenic gene adrenomedullin (ADM), which was found to be upregulated in the stroma of cervical cancer and which localized mainly in the blood and lymphatic vessels, was identified as a target of inhibition by miR-126 at the carcinoma in situ-to-invasion stage. The study suggests a cancer stroma cross talk induced repression of miR-126 and upregulation of ADM, and probably other proangiogenic factors, to facilitate angiogenesis and invasion growth of cervical cancer.

優秀論文獎編號: PhD19

Teroxirone inhibited growth of human non-small cell lung cancer cells by activating p53

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In this work, we demonstrated that the growth of human non-small-cell-lung-cancer cells H460 and A549 cells can be inhibited by low concentrations of an epoxide derivative, teroxirone, in both in vitro and in vivo models. The cytotoxicity was mediated by apoptotic cell death through DNA damage. The onset of ultimate apoptosis is dependent on the status of p53. Teroxirone caused transient elevation of p53 that activates downstream p21 and procaspase-3 cleavage. The presence of caspase-3 inhibitor reverted apoptotic phenotype. Furthermore, we showed the cytotoxicity of teroxirone in H1299 cells with stable ectopic expression of p53, but not those of mutant p53. A siRNA-mediated knockdown of p53 expression attenuated drug sensitivity. The in vivo experiments demonstrated that teroxirone suppressed growth of xenograft tumors in nude mice. Being a potential therapeutic agent by restraining cell growth through apoptotic death at low concentrations, teroxirone provides a feasible perspective in reversing tumorigenic phenotype of human lung cancer cells.

優秀論文獎編號: PhD20

Hypomethylation signature of tumor-initiating cells predicts poor prognosis of ovarian cancer patients

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DNA methylation contributes to tumor formation, development, and metastasis. Epigenetic dysregulation of stem cells is thought to predispose to malignant development. The clinical significance of DNA methylation in ovarian tumor-initiating cells (OTICs) remains unexplored. We analyzed the methylomic profiles of OTICs (CP70sps) and their derived progeny using a human methylation array. qRT-PCR, quantitative methylation-specific PCR (qMSP), and pyrosequencing were used to verify gene expression and DNA methylation in cancer cell lines. The methylation status of genes was validated quantitatively in cancer tissues and correlated with clinicopathological factors. *ATG4A* and *HIST1H2BN* were hypomethylated in OTICs. Methylation analysis of *ATG4A* and *HIST1H2BN* by qMSP in 168 tissue samples from patients with ovarian cancer showed that *HIST1H2BN* methylation was a significant independent predictor of progression-free survival (PFS) and overall survival (OS). Multivariate Cox regression analysis showed that patients with a low level of *HIST1H2BN* methylation had poor PFS (HR, 4.5; 95% CI, 1.4–14.8) and OS (HR, 4.3; 95% CI, 1.3–14.0). Hypomethylation of both *ATG4A* and *HIST1H2BN* predicted a poor PFS (HR, 1.8; 95% CI, 1.0–3.6; median, 21 months) and OS (HR, 1.7; 95% CI, 1.0–3.0; median, 40 months). In an independent cohort of ovarian tumors, hypomethylation predicted early disease recurrence (HR, 1.7; 95% CI, 1.1–2.5) and death (HR, 1.4; 95% CI, 1.0–1.9). The demonstration that expression of *ATG4A* in cells increased their stem properties provided an indication of its biological function. Hypomethylation of *ATG4A* and *HIST1H2BN* in OTICs predicts a poor prognosis for ovarian cancer patients.

優秀論文獎編號: PhD21

Epigenetic silencing of PTPRR activates MAPK signaling, promotes metastasis and serves as a biomarker of invasive cervical cancer

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Epigenetic modifications are a driving force in carcinogenesis. However, their role in cancer metastasis remains poorly understood. The present study investigated the role of DNA methylation in cervical cancer metastasis. Here, we report evidence of the overexpression of DNA methyltransferases 3B (DNMT3B) in invasive cervical cancer and of the inhibition of metastasis by DNMT3B interference. Using methyl-DNA immunoprecipitation coupled with microarray analysis (mDIP-on-chip), we found that the protein tyrosine phosphatase receptor type R (PTPRR) was silenced through DNMT3B-mediated methylation in cervical cancer. PTPRR inhibited p44/42 MAPK signaling, the expression of the transcription factor AP1, human papillomavirus (HPV) oncogenes E6/E7, and DNMTs. The methylation status of PTPRR increased in cervical scrapings (n = 358) in accordance with disease severity, especially in invasive cancer. Methylation of the PTPRR promoter plays an important role in the metastasis and may be a biomarker of invasive cervical cancer.

已通過之專利:

名稱：一種癌症的篩檢方法 Cancer Screening Method:

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優秀論文獎編號: PhD22

Prostate cancer-derived CCN3 induces M2 macrophage infiltration and contributes to angiogenesis in prostate cancer microenvironment

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Tumor-associated macrophages (TAMs) are M2-polarized macrophages that infiltrate the tumor microenvironment and promote tumorigenesis. However, the mechanisms by which TAMs modulate prostate cancer (PCa) growth are poorly understood. Here, we found that expression of Nephroblastoma Overexpressed (NOV/CCN3) is upregulated in PCa cells and correlated with M2 macrophage infiltration. RAW264.7 macrophage migration was induced by conditioned media (CM) from various PCa cells in proportion to the cellular level of CCN3 expression and was inhibited by an anti-CCN3 neutralizing antibody. CCN3 and PCaCM treatment skewed RAW264.7 cell differentiation from an M1 phenotype to an M2 phenotype. PCa-derived CCN3 induced focal adhesion kinase (FAK)/Akt/NF-κB signaling in RAW264.7 cells, which resulted in VEGF expression and subsequently increased tube formation in endothelial progenitor cells. Finally, PCa-secreted CCN3 stimulated RAW264.7 cells and promoted angiogenesis in the chick chorioallantoic membrane assay (CAM), and increased tumor growth and tumor-associated angiogenesis in a PCa xenograft mouse model. Our results indicate that PCa-secreted CCN3 can recruit macrophages and skew their differentiation to an M2 phenotype. In turn, CCN3-stimulated macrophages contribute to VEGF-dependent angiogenesis. This study reveals a novel mechanism by which TAMs enhance PCa angiogenesis and identifies a potential therapeutic target for PCa.

優秀論文獎編號: PhD23

Suppression of the *SOX2* neural effector gene by PRDM1 promotes human germ cell fate in embryonic stem cells

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The mechanisms of transcriptional regulation underlying human primordial germ cell (PGC) differentiation are largely unknown. The transcriptional repressor Prdm1/Blimp-1 is known to play a critical role in controlling germ cell specification in mice. Here, we show that PRDM1 is expressed in developing human gonads and contributes to the determination of germline versus neural fate in early development. We show that knockdown of PRDM1 in human embryonic stem cells (hESCs) impairs germline potential and upregulates neural genes. Conversely, ectopic expression of PRDM1 in hESCs promotes the generation of cells that exhibit phenotypic and transcriptomic features of early PGCs. Furthermore, PRDM1 suppresses transcription of *SOX2*. Overexpression of *SOX2* in hESCs under conditions favoring germline differentiation skews cell fate from the germline to the neural lineage. Collectively, our results demonstrate that PRDM1 serves as a molecular switch to modulate the divergence of neural or germline fates through repression of *SOX2* during human development.

優秀論文獎編號: PhD24

Regulation of mitochondrial F_oF_1ATPase activity by Sirt3-catalyzed deacetylation and its deficiency in human cells harboring 4977bp deletion of mitochondrial DNA

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Sirt3, a mitochondrial NAD(+)-dependent deacetylase, is regarded as a potential regulator in cellular metabolism. However, the role of Sirt3 in the regulation of mitochondrial F_oF_1ATPase and the linkage to mitochondrial diseases is unclear. In this study, we demonstrated a role of Sirt3 in the regulation of F_oF_1ATPase activity in human cells. Knockdown of Sirt3 in 143B cells by shRNA transfection caused increased acetylation levels of the α and OSCP subunits of F_oF_1ATPase. We showed that Sirt3 physically interacted with the OSCP and led to its subsequent deacetylation. By incubation of mitochondria with the purified Sirt3 protein, Sirt3 could regulate F_oF_1ATPase activity through its deacetylase activity. Moreover, suppression of Sirt3 reduced the F_oF_1ATPase activity, consequently decreased the intracellular ATP level, diminished the capacity of mitochondrial respiration, and compromised metabolic adaptability of 143B cells to the use of galactose as the energy source. In human cells harboring ≅85% of mtDNA with 4977bp deletion, we showed that oxidative stress induced a reduction of Sirt3 expression, and an increased acetylation of the OSCP subunit of F_oF_1ATPase. Importantly, the expression of Sirt3 was also decreased in the skin fibroblasts from patients with CPEO syndrome. We further demonstrated that oxidative stress induced by 5-10μM of menadione impaired the Sirt3-mediated deacetylation and activation on F_oF_1ATPase activity through decreasing the protein level of Sirt3. Our findings suggest that increased intracellular ROS levels might modulate the expression of Sirt3 which deacetylates and activates F_oF_1ATPase in human cells with mitochondrial dysfunction caused by a pathogenic mtDNA mutation.

優秀論文獎編號: PhD25

Chemotherapeutic sensitivity of testicular germ cell tumors under hypoxic conditions is negatively regulated by SENP1-controlled sumoylation of OCT4.

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Testicular germ cell tumors (TGCT) generally respond well to chemotherapy, but tumors that express low levels of the transcription factor OCT4 are associated with chemoresistance and poor prognosis. Hypoxia is known to induce drug resistance in TGCTs; however, the mechanistic basis for reduced expression of OCT4 and drug resistance is unclear. Here we show that hypoxia reduces OCT4 levels and increases the resistance of embryonal carcinoma (EC) cells to cisplatin and bleomycin. Furthermore, we show that the loss of OCT4 expression under hypoxia can be triggered by sumoylation, which was regulated by SUMO1 and the SUMO1 peptidase SENP1. Under hypoxic conditions, overexpression of SUMO1gg (the active form of SUMO1) not only increased the level of sumoylated OCT4 (Su-OCT4), but also decreased the stability of OCT4 protein. In addition, overexpression of SENP1 reduced the Su-OCT4 level induced by SUMO1gg overexpression, thereby maintaining OCT4 levels and enhancing chemosensitivity. Mechanistic investigations revealed that OCT4 sumoylation occurred at K123, as overexpression of an OCT4-K123R mutant effectively reduced the level of Su-OCT4 under hypoxic conditions. Taken together, our results showed that hypoxia reduces OCT4 expression levels in ECs to increase drug resistance and that these effects could be countered to ablate the suppressive effects of hypoxia on chemosensitivity. Our findings also highlight SENP1 as a potential therapeutic target for drug resistant TGCTs.

優秀論文獎編號: PhD26

Innovative strategy with potential to increase hemodialysis efficiency and safety

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Uremic toxins are mainly represented by blood urine nitrogen (BUN) and creatinine (Crea) whose removal is critically important in hemodialysis (HD) for kidney disease. Patients undergoing HD have a complex illness, resulting from: inadequate removal of organic waste, dialysis-induced oxidative stress and membrane-induced inflammation. Here we report innovative breakthroughs for efficient and safe HD by using a plasmon-induced dialysate comprising Au nanoparticles (NPs)-treated (AuNT) water that is distinguishable from conventional deionized (DI) water. The diffusion coefficient of $K_3Fe(CN)_6$ in saline solution can be significantly increased from 2.76 to 4.62 × 10^{-6} cm s^{-1}, by using AuNT water prepared under illumination by green light-emitting diodes (LED). *In vitro* HD experiments suggest that the treatment times for the removals of 70% BUN and Crea are reduced by 47 and 59%, respectively, using AuNT water instead of DI water in dialysate, while additionally suppressing NO release from lipopolysaccharide (LPS)-induced inflammatory cells.

優秀論文獎編號: MS4

Putative oncogene *UBE1C* inhibits the transcription activity of p53 in lung cancer

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Background: In view of the therapeutic benefits resulting from early intervention for Fabry disease, our team has implemented an enzyme-based newborn screening in Taiwan since 2008. However, we found that most heterozygous females cannot be detected. To improve the screening efficiency, a more effective method for *GLA* gene genotyping is necessary.

Methods: As the suspected mutations are limited to only 29 different spots in Taiwanese, a panel of Sequenom iPLEX assay was designed for rapid screening of *GLA* variations. To determine the accuracy and sensitivity of this assay, previously diagnosed and undiagnosed DNA samples were analyzed by this genotyping assay and Sanger sequencing. In addition, DNA extracted from dried blood spots was also tested.

Results: Sequenom iPLEX assay is accurate and cost-effective, identifying the sequence variations, which were designated in the panel. It identified common *GLA* variants in DNA samples extracted from whole blood or dried blood spots with 100% accuracy and sensitivity.

Conclusions: Sequenom iPLEX assay is suitable for Fabry newborn screening when hotspot mutations and common variations are known in a well-studied population. In addition, this assay can also be applied for first-line determination of *GLA* variant sequences in suspected subjects of high-risk patients, or newborns.

Keywords: Fabry disease; Sequenom's MassARRAY®; Sequenom iPLEX assay; *GLA* genotyping.

優秀論文獎編號: MS6

Quantitative apical membrane proteomics reveals vasopressin-induced actin dynamics in collecting duct cells

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In kidney collecting duct cells, filamentous actin (F-actin) depolymerization is a critical step in vasopressin-induced trafficking of aquaporin-2 to the apical plasma membrane. However, the molecular components of this response are largely unknown. Using stable isotope-based quantitative protein mass spectrometry and surface biotinylation, we identified 100 proteins that showed significant abundance changes in the apical plasma membrane of mouse cortical collecting duct cells in response to vasopressin. Fourteen of these proteins are involved in actin cytoskeleton regulation, including actin itself, 10 actin-associated proteins, and 3 regulatory proteins. Identified were two integral membrane proteins (Clmn, Nckap1) and one actin-binding protein (Mpp5) that link F-actin to the plasma membrane, five F-actin end-binding proteins (Arpc2, Arpc4, Gsn, Scin, and Capzb) involved in F-actin reorganization, and two actin adaptor proteins (Dbn1, Lasp1) that regulate actin cytoskeleton organization. There were also protease (Capn1), protein kinase (Cdc42bpb), and Rho guanine nucleotide exchange factor 2 (Arhgef2) that mediate signal-induced F-actin changes. Based on these findings, we devised a live-cell imaging method to observe vasopressin induced F-actin dynamics in polarized mouse cortical collecting duct cells. In response to vasopressin, F-actin gradually disappeared near the center of the apical plasma membrane while consolidating laterally near the tight junction. This F-actin peripheralization was blocked by calcium ion chelation. Vasopressin-induced apical aquaporin-2 trafficking and forskolin-induced water permeability increase were blocked by F-actin disruption. In conclusion, we identified a vasopressin-regulated actin network potentially responsible for vasopressin-induced apical F-actin dynamics that could explain regulation of apical aquaporin-2 trafficking and water permeability increase.

103 年度第 11 屆壁報展示獎摘要

壁報展示獎編號: **MS1**

Transcriptional activation of pentraxin-3 gene expression is associated with EGF-induced head and neck cancer cell metastasis

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Overexpression of epidermal growth factor receptor (EGFR) and production of proinflammatroy cytokines are well clarified in head and neck squamous cell carcinoma (HNSCC) and correlates with enhanced invasion and metastasis. However, molecular mechanisms involved in activation of EGFR and productions of cytokines in regulating metastasis of HNSCC remain poorly understood. Here, we identified PTX3 as a metastasis-promoting factor to mediate EGF-induced HNSCC metastasis. Analysis of PTX3 expression between normal and malignant or metastatic tissues from HNSCC patients was performed using published datasets, indicating that expression level of PTX3 in malignant tissues was higher than in normal part in HNSCC patients. We found that EGF induced transcriptional activation of PTX3 by activating the binding of c-Jun and NF-κB factors to AP-1 binding site of the PTX3 promoter. The downstream of EGFR pathways, PI3K/AKT and NF-κB were essential for the induction of PTX3. In addition, EGF- induced PTX3 expression was significantly inhibited in c-Jun and NF-κB knockdown cells. EGF stimulated the secretion of PTX3 from cancer cell, resulting in enhancing cell migration and invasion. Effects of EGF on the induction of fibronectin and MMP9 expression, and inhibition of E-cadherin were abolished in PTX3 knockdown cells. These findings reveal the mechanism that autocrine production of EGF-induce PTX3-regulated HNSCC metastasis was through enhancing metastatic molecules, such as fibronectin and MMP9 expression. Induction of PTX3 possibly reflecting the EGFR-caused HNSCC metastasis associated with inflammation.

壁報展示獎編號: MS2

Annexin A2 regulates epithelial-mesenchymal transition and therapeutic tolerance in nasopharyngeal carcinoma

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Nasopharyngeal carcinoma (NPC), originated from the epithelium of the nasopharynx, is a common malignant tumor. NPC mainly occurs in the Southeast Asia including Taiwan. Characteristically, NPC is different from other head and neck carcinomas, especially for its high metastasis character and poor efficiency of clinical treatment. Recently, many reports have indicated that annexin A2 might regulate the metastasis on different kinds of cancer. However, the tumorigenic function of annexin A2 in NPC is not yet understood. According to our data, the level of annexin A2 highly expressed on NPC patient tissues by using immunohistochemistry (IHC). Annexin A2 shRNAs were used to evaluate the effects of annexin A2 suppression on NPCs. Silencing annexin A2 protein reduces the cell proliferation both *in vivo* and *in vitro*. Moreover, annexin A2 regulates the tolerance to chemo drugs (Cisplatin, 5-FU, Vincristine and Docetaxel) and irradiation. From chemo drug killing assay and radio survival assay, annexin A2 knockdown cell line (781) shows more sensitive to chemo- and radio reaction compared to scramble control. Furthermore, Annexin A2 not only up-regulates cell adhesion, migration, and invasion abilities on NPCs, but also involves in epithelial-mesenchymal transition (EMT). In summary, annexin A2 regulates the EMT pathway and therapeutic tolerance in NPCs. We believe that annexin A2, on nasopharyngeal carcinoma, may be a prognosis target during clinical therapy.

壁報展示獎編號: MS3

Role of EPAEE in improving response and specific target drug sensitivity in KRAS mutated cells

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EPA ethyl ester (EPAEE) is known easily absorbed and obtained from fatty fish. In current study, we provide a possible therapeutic strategy to the colorectal cancer (CRC), which was known when the cells contain with the KRAS mutant is a activating predominate mechanism of resistance to EGFR inhibitors, Erbitux. According to our pervious findings, up-regulated the expression of miR-A by intaking lauric acid in mutant CRC cells would further triggered the cells sensitive to Erbitux. Herein, we used FDA-approved EPAEE instead of lauric acid, and try to give a practical purpose of clinical application. We hypothezied that increase the concentration of EPAEE might result in the cell proliferation, which might modulate expression of miR-A, and further effect the protein phosphorylation of ERK1/2, and then further trigger the effect of Erbitux to mutants CRC cells. Obviously, higher expression of miR-A could be detected after treated with 40μM EPAEE for 24 hours in all type of mutated cells except control wild type CRC cells. In addition, the lower cell survival rate has been observed in the 0.2μM of Erbitux treatment, especially in the KRAS mutants and control wild type cells ($p = 0.010 \sim 0.013$). Interestingly, the higher phosphorylated proteins level of ERK1/2 could be noted in KRAS EPAEE-fed cells ($p = 0.006 \sim 0.047$), although the total protein was shown lower expression level ($p = 0.035$); but opposite result was shown in BRAF EPAEE-fed mutants when compared to original cells. Consist of higher Erbitux response rate in KRAS mutants and even in Caco-2 could also be found. However, less evidences in BRAF mutant CRC cells could be observed might result from few case collections. Indeed, unclear bio-mechanism of EPAEE need to be further proved. In conclusion, up-regulation of the miR-A induced by EPAEE might further lead KRAS mutant cells significantly restored the sensitivity to Erbitux. Our findings might offer great potential of therapeutic solution for future clinical CRC patients.

壁報展示獎編號: MS5

To study the role of CCN1 in neointima formation

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CCN1 (Cyr61), an extracellular matrix protein, is involved in diverse and sometimes opposing cellular activities through binding to a variety of integrins in different cell types and contexts. Vascular remodeling occurs preferentially at branched or curved arteries with disturbed flow leading to low and oscillatory wall shear stress. Despite the close association between CCN1 and neointima formation, the role of CCN1 in neointima formation-induced by disturbed flow is not clear. In this study, we used the mouse models induced by complete carotid artery ligation to identify the role of CCN1 in neointima formation. First, *Ccn1*$^{+/LacZ}$ mice, in which a LacZ gene was inserted in the *Ccn1* genomic locus to be driven by *Ccn1* promoter, were used to identify the CCN1 expression in neointima formation after carotid artery ligation. After ligation, CCN1 was expressed in neointima and media of the ligated artery. We will use the markers of endothelial cell, smooth muscle cell and macrophage to identify the types of cells expressing CCN1. Second, we speculate CCN1 may affect the neointima formation via binding to integrin α6β1, so we used *Ccn1*$^{dm/dm}$ mice (DM), which express α6β1-binding deficient CCN1 protein. After ligation, we found that the neointima area in DM mice was less developed than in WT mice. This result indicated that α6β1-binding deficient mutation of *Ccn1* attenuates neointima formation following blood flow cessation. Next, to understand how CCN1 reduces neointima formation, we will use immunofluorescence staining to indicate whether CCN1 mediates the expression of adhesion molecules, immune cells infiltration, the secretion of inflammatory cytokines, and proliferation and apoptosis of vascular cells through binding to α6β1. In conclusion, our findings indicate that CCN1 is a critical pathophysiological regulator mediating neointima formation induced by complete carotid artery ligation.

壁報展示獎編號: MS7

Heart rate variability as a prognostic indicator of emotional disorders in patients with mild traumatic brain injury

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Depression and anxiety are the most frequently diagnosed emotional disorders after a mild traumatic brain injury (mTBI); however, predictors of these disorders after an mTBI remain uncertain. Recent research indicated that depression and anxiety are associated with abnormalities in the autonomic nerve system (ANS) which controls heart rate variability (HRV). One analytical algorithm, the frequency-domain analysis of HRV, has gained in popularity with broad applications as a functional index of the ANS. In this study, we investigated whether a power spectrum analysis of HRV can predict the occurrence of emotional disorders such as depression and anxiety in mTBI patients.

The research group consisted of mTBI patients and healthy volunteers from our affiliated hospitals. Two important psychological evaluations, the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI), were used as part of 6- and 12-week follow-up assessments. For both the patient and volunteer groups, we recorded individuals' 5-min resting assessment of HRV. Results showed some significant correlations in serum biomarkers and HRV parameters between healthy volunteers and mTBI patients. The findings also indicated that mTBI patients were vulnerable to emotional disorders, compared to healthy controls, as evaluated by the BAI and BDI scores. In spite of the small sample size, these results also have implications as a potential method for predicting whether mTBI patients are susceptible to emotional disorders using an HRV analysis.

壁報展示獎編號: MS8

The effect of *Platycodon grandiflorus* on glucose uptake

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The prevalence of metabolic syndrome has been increasing dramatically due to the sedentary lifestyle and the diet rich in fat and sugar. According to previous research, Saponins isolated from the root of *P. grandiflorus* have showed novel pharmacological effects such as anti-hyperglycemia and anti-lipidemia. It is known when activating insulin receptor (IR), insulin induces signaling pathway through IRS-1 (Insulin receptor substrate 1), PDK (Phosphoinositide-dependent kinase-1), AKT (Protein Kinase B) and then enhancing the uptake of glucose through translocation of GLUT4 vesicles from cytoplasm to the cell membrane. In this study, we demonstrated that *P. grandiflorus* extract induced phosphorylation of IR, IRS-1, PDK, AKT in C_2C_{12} myotube using the western blotting analysis. In the glucose uptake experiment, *P. grandiflorus* extract improved glucose uptake in cells using ^{3}H-glucose. In addition, the extract also had the beneficial effects on decreasing blood sugar in STZ/nicotinamide-treated mice. In conclusion, *P. grandiflorus* extract could regulate glucose homeostasis in type 2 diabetes.

壁報展示獎編號: MS9

The extract of Dioscorea opposita determines the effect on regulating blood sugar *in vivo*

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The metabolic syndrome has received a great attention in recent years. The diet with high calories is considered as the risking factors for obesity, hypertension, high triglycerides and hyperglycemia. *Dioscorea opposita* had been reported to have beneficial effects on diabetes in ancient *Chinese pharmacopoeia*. We screened four hundred herbal extracts and found *Dioscorea opposita* extract could improve blood sugar level significantly. The purpose of this study was to investigate how *Dioscorea opposita* to regulate blood sugar. In cell experiments, the phosphorylations of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) were increased in differentiated C_2C_{12} myotubes that were treated with aqua-extract of *Dioscorea opposita*. In addition, the phosphorylations of Insulin receptor substrate 1 (IRS1), Protein Kinase B (AKT) and S6 kinase 1 (S6K1) were also up-regulated in cells. In animal study, the extract was shown to lower plasma triglyceride level, visceral fat, and weight in the STZ/nicotinamide-induced-diabetic mice fed with high-fat diet. Furthermore, the extract also ameliorated hyperglycemia and improved glucose tolerance in the mice. In conclusion, *Dioscorea opposita* could have beneficial effects on anti-hyperglycemic and anti-obesity.

壁報展示獎編號: **MS10**

Roles of spleen tyrosine kinase in IL-17-induecd CCL20 chemokine expression in keratinocytes

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Interleukin-17A (IL-17A) is one of the Th17 cytokines and plays an important role in the immunopathogenesis of autoimmune diseases such as psoriasis. Up to date, accumulating evidence has strongly revealed the clinical benefits of inhibition of IL-17A for psoriasis treatment. Syk is a non- receptor tyrosine kinase and has been implicated as a critical mediator in various immune stimulation. Nevertheless, little is known about the relationship of Syk in skin disease and IL-17A signaling. Therefore in this study we used IL-17A-stimulated expression of CC chemokine ligand 20 (CCL20) in normal human epidermal keratinocytes as a cell model to investigate the role of Syk in this aspect. We found that IL-17A stimulation can induce CCL20 gene and protein expression in time- and concentration-dependent manners. Moreover, the activation of IKK, NF-κB, JNK and Syk were observed during IL-17A stimulation. By treating cells with TAK inhibitor and Syk siRNA, we found Syk is an upstream signal molecule of TAK. Inhibition of Syk strikingly attenuated all signal kinases activation and CCL20 secretion induced by IL-17A. Data of promoter activity assay combined with site-directed mutagenesis of CCL20 reporter construct further showed that IL-17A-elicited CCL20 upregulation is depending on Syk-mediated NF-κB pathway. Data using immunoprecipitation also indicated the interaction of Syk with IL-17R downstream signal components such as TRAF6 and Act1 under IL-17A stimulation. However, the essential signaling interaction of TRAF6 and Act1 under IL-17A stimulation was diminished when Syk expression was repressed by siRNA approach. Lastly, using immunocomplex kinase assay we demonstrated that Syk can mediate TRAF6 phosphorylation. Taken together, we for the first time identify Syk as an upstream signaling regulator in IL-17R-mediated Act1-TRAF6 interaction, and demonstrate that Syk plays an essential role for IL-17R-stimulated NF-κB activation and CCL20 gene transcription in primary human keratinocytes. All these findings not only unmask a new role of Syk in IL-17A-mediated inflammatory response, but also shed a new light into the potential therapeutic target of Syk in psoriasis.

壁報展示獎編號: **MS11**

Antroquinonol suppresses breast tumor migration/invasion through inhibiting ERK/AP-1- and AKT/NF-κB-dependent MMP-9 and epithelial-mesenchymal transition expressions

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Antroquinonol (ANQ) is an ubiquinon derivative isolated from *Antrodia camphorata*. However, the effect of ANQ on breast cancer treatment is unknown. We found that ANQ significantly suppressed the migration and invasion of breast cancer MDA-MB-231 cells, and inhibited 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced invasiveness by MCF7 cells. ANQ inhibited MMP-9 gene expression and enzymatic activity. Inhibition of ERK and AKT blocked TPA-elicited MMP-9 protein expression, and the addition of ANQ suppressed phosphorylation of ERK and AKT. The induction of the AP-1 and NF-κB pathway participated in MMP-9 transcription. Suppression of ERK inhibited AP-1, whereas blocking AKT diminished NF-κB activity, and treatment with ANQ suppressed both AP-1 and NF-κB signaling. Moreover, ANQ suppressed EMT proteins expression, and inhibited TPA-induced EMT through downregulating the ERK/AP-1 and AKT/NF-κB signaling cascades. Together, our data showed for the first time that ANQ inhibited breast cancer invasiveness by suppressing ERK/AP-1- and AKT/NF-κB-dependent MMP-9 and EMT expressions.

壁報展示獎編號: MS12

Cooperation of CD49f and IGF-1R signaling in maintenance of pluripotent transcription factor Oct4 of alkaline phosphatase positive mouse germline stem cells

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Introduction：Stem cell niche is known to regulate germline stem cells (GSCs) self-renew and differentiation of germline stem cells (GSCs). Our previously studies has reported that insulin like growing factor 1 receptor (IGF-1R) signaling pathway and CD49f are able to maintain the Oct-4 levels in GSCs. However, the CD49f and IGF-1R downstream regulator that directly regulates the Oct-4 expression in nucleus is still unclear. Hypoxia induce factor 2α (HIF-2α) known to be induced by hypoxia stress; and the HIF-2α can bind Oct-4 promoter induce Oct-4 protein expression in nucleus. The aim of this study is to examine whether IGF-1R and CD49f signaling regulate the Oct-4 expression in mouse GSCs through HIF-2α.

Materials and Methods: CD49f positive mice GSCs were purified by magnetic-activated cell sorting (MACS) and have been confirmed has strong alkaline phosphatase (AP) activity, called $CD49f^{+}AP^{+}$GSCs. The GSCs was cultured in laminin-coated plate.

Results: We observed IGF-1 dose-dependently increased the expression of HIF-2α as well as the Oct-4 in $CD49f^{+}AP^{+}$GSC cells. Moreover, experiments using signal inhibitors such as LY2940002 (PI3K inhibitor) and Rapamycin (mTOR inhibitor) effectively suppressed the IGF-1-induced HIF-2α and Oct-4 expression in GSCs. Meanwhile, we also found out picropodophyllin (PPP, a specific inhibitor of IGF-IR phosphoylation) had lower inhibit ability as well as shIGF-1R so that we suspected there were another signal pathway modulated IGF-1 downstream signal. So we hypothesized CD49f cooperated with IGF-1R on Oct-4 maintenance through PI3K/Akt/mTOR/HIF-2α in $CD49f^{+}AP^{+}$GSC. In our result, inhibition of CD49f by siRNA indicated Akt/mTOR were downregulated. We suppressed CD49f and IGF-1R through transfected siCD49f and shIGF-1R, and discovered HIF-2α and Oct-4 were restrained obviously.

Conclusion: In our conclusion, CD49f would crosstalk with IGF-1R to regulate Oct-4 expression.

壁報展示獎編號: **MS13**

Oridonin inhibits RNA transportation to induce glioma cell apoptosis via down-regulation of RanGAP1 expression

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Nuclear RanGTP-RNA complex would be hydrolyzed by Ran GTPase activating protein 1 (RanGAP1), and result in the release of RNA into cytoplasm. In this study, 5-30 μM of oridonin, a natural diterpenoid compound isolated from traditional Chinese medicine *R. rubescens*, induced U87MG glioma cells apoptosis and RNA accumulation in nucleus. After treatment of oridonin, RanGAP1 protein amount was decreased and RanGTP was accumulated in nucleus as investigated using immunoprecipitation and immunofluorescence, respectively, suggesting that down-regulation of RanGAP1 protein level would reduce RNA export via entrapment of RanGTP in nucleus. Over-expression of RanGAP1 protein reversed oridonin-induced U87MG cell death. Hence, we demonstrated for the first time that down-regulation of RanGAP1 protein level by oridonin results in RNA accumulation in nucleus which even lead to cell apoptosis in glioma cells.

壁報展示獎編號: **MS14**

Identification gene candidates of kinase downstream signaling regulated by Flavonoid Luteolin in A431-III cells using transcriptome-based analysis

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Flavonoids luteolin is a multiple kinase inhibitor and be used for inhibit tumor cell migration, invasion and angiogenesis. Flavonoids lutrolin and quercetin block EMT transition and NF-kB signaling to inhibit the greater invasion ability of A431-III cells. The kinase signaling regulates downstream gene transcription to affect invasion abilities of tumor cells. Flavonoids are reported as variety of anticancer inhibits, such as cell growth, apoptosis induction, differentiation and kinase inhibition. We reports the transciptiome-based analysis gene transcription treated with Flavonoids luteolin in A431-III cells. Highly transcription changed genes are identified, including up-regulated and down-regulated genes. These genes are the downstream targets of multiple kinases signaling, including Akt, NF-kB, Apoptosis, ribosome biogenesis and metabolic pathway. Some of these genes are reported highly expression in several malignancy tumors and contributes to tumor formation and invasion. Western blot analysis and kinase inhibitors are used to identify the kinase pathways inhibited by luteolin. Collectively, we reports a whole genome genes transcription differentially inhibited by Flavonoids luteolin in A431-III cells to identified downstream target genes. These genes may contribute to highly invasion abilities of A431-III cells and as novel biomarkers for clinical diagnosis and therapeutic targets.

壁報展示獎編號: MS15

Evaluate Ca2+-r-PGA in wound healing application on human skin cells by ToF-SIMS

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Understanding wound healing today involves much more than simply stating that there are three phases: "inflammation, proliferation, and maturation." Wound healing is a complex series of reactions and interactions among cells and "mediators. [1] In this study, calcium form r-PGA (Ca^{2+}-r-PGA) was selected as a mediator agent for wound healing. The r-PGA's physical factors are realty affected by humidity and have high hydrophilic property, excellent water-binding capacity, fine swelling ability and biocompatibility. [2] Through the advantages, during the past decade, r-PGA has been used in suitable for clinical fields. Cellular responses in wound healing cascade are associated with change in the extracellular calcium. In this study, human skin cells (CCD-966SK) were treated with Ca^{2+}-r-PGA. The in vitro biological behavior, cell affinity, as well as, the biodegradability (including cell survival, cell toxicity and cell apoptosis) was evaluated. Besides, the human skin cells of Ca^{2+} distribution was observed by ToF-SIMS. According to the preliminary results, we found that Ca^{2+}-r-PGA has potential efficacy as wound healing material.

財團法人台北市林榮耀教授學術教育基金會
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第十屆 (102年)

優秀論文獎得獎人

姓名	單位	指導教授	論文題目	學術刊物
林暉皓	國立清華大學生物科技研究所	江安世	Parallel Neural Pathways Mediate CO2 Avoidance Responses in *Drosophila*	Science
魏珮琪	國防醫學院生命科學研究所	李文華	The role of NPGPx in ER stress response	Molecular Cell
白宗彬	國立清華大學生物科技研究所	江安世	Drosophila ORB protein in two mushroom body-output neurons is necessary for long-term memory formation	Proceedings of the National Academy of the Sciences of the United States of America
林意棟	國立成功大學醫工所	謝清河	Instructive nanofiber scaffolds with VEGF create a microenvironment for arteriogenesis and cardiac repair	Science Translational Medicine
王立傑	長庚大學生物醫學研究所	張玉生	Interactome-wide analysis identifies end-binding protein 1 as a crucial component for the speck-like particle formation of activated AIM2 inflammasomes	Molecular & Cellular Proteomics

壁報展示獎得獎人

姓名	單位	指導教授	論文題目	學術刊物
王亮傑	國立台灣大學生化科學研究所	陳宏文	High-temperature requirement protein A4 (HtrA4) suppresses the fusogenic activity of syncytin-1 and promotes trophoblast invasion	Molecular & Cellular Biology
冉毅驊	國立清華大學生物資訊與結構生物研究所	蕭宏昇	Adenylate kinase-4 is a marker of poor clinical outcomes that promotes metastasis of lung cancer by downregulating the transcription factor ATF3	Cancer Research
劉家宏	國立台灣大學生醫電子與資訊學研究所	黃奇英	Analysis of Protein-Protein Interactions in Cross-talk Pathways Reveals CRKL Protein as a Novel Prognostic Marker in Hepatocellular Carcinoma	Molecular & Cellular Proteomics
姜寧	國立台灣大學分子與細胞生物學研究所	王致恬	Cysteine string protein-α regulates fusion pore dynamics during calcium-dependent exocytosis via changing its phosphorylated state	-
周廷蓁	國立成功大學生物化學暨分子生物學研究所	陳昌熙	Enterohaemorrhagic *Escherichia coli* O157:H7 Shiga-like toxin 1 is required for full pathogenicity and activation of the p38 mitogen-activated protein kinase pathway in *Caenorhabditis elegans*	-
施詠馨	國立成功大學藥理學研究所	王憶卿	Putative Oncogene UBE1C Inhibits the Transcription Activity of p53 in Lung Cancer	-
詹雅衣	國立成功大學藥理學研究所	陳炳焜	The potential role of ARNT in the regulation of cisplatin-induced cancer cell death	-
陳其欣	國立成功大學藥理學研究所	王憶卿	Oct4-Mediated Transcriptional Deregulation Promotes Lung Tumor Progression and Drug-Resistance	-

財團法人台北市林榮耀教授學術教育基金會
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第九屆 (101年)

優秀論文獎得獎人

姓名	單位	指導教授	論文題目	學術刊物
林士鳴	國立清華大學生物資訊與結構生物研究所	潘榮隆	Crystal structure of a membrane-embedded H+-translocating pyrophosphatase	Nature 484: 399–403 (2012)
楊文豪	國立陽明大學臨床醫學研究所	楊慕華	RAC1 activation mediates Twist1-induced cancer cell migration	Nature Cell Biology 14 (4): 366-74 (2012)
潘羿汝	國立中興大學生命科學系	陳鴻震	FAK is required for assembly of podosome rosettes	Journal of Cell Biology 195: 113-129 (2011)
黃尉倫	陽明大學生化暨分子生物研究所	王學偉	Snail Regulates Interleukin-8 Expression, Stem-Cell–Like Activity, and Tumorigenicity of Human Colorectal Carcinoma Cells	Gastroenterology 141:279-291 (2011)
黎思宇	國立清華大學生物科技研究所	江安世	Auditory Circuit in the Drosophila Brain	Proc Natl Acad Sci USA 109: 2607-2612 (2012)

壁報展示獎得獎人

姓名	單位	指導教授	論文題目	學術刊物
林家靖	陽明大學生物化學暨分子生物研究所	陳志成	An antinociceptive role for Substance P in acid-induced chronic muscle pain	Proc Natl Acad Sci USA 109 (2): E76-83 (2012)
楊盈盈	國立陽明大學公共衛生研究所	林明薇	Association of the G-protein and alpha-2 adrenergic receptor gene and plasma norepinephrine level with clonidine improvement of effects of diuretics in cirrhotic patients with refractory ascites: a randomized clinical trial	Gut 59: 1545-53 (2010)
楊長青	長庚大學生物醫學所	譚賢明	Epigenetic silencing of myogenic gene program by Myb-binding protein 1a suppresses myogenesis	The EMBO Journal 31, 1739-1751 (2012)
張慈華	國防醫學院醫學科學研究所	楊泮池	Slug confers resistance to the epidermal growth factor receptor tyrosine kinase inhibitor	American Journal of Respiratory and Critical Care Medicine 183 (8): 1071-9 (2011)
陳鈺杰	台灣大學分子與細胞生物學研究所	王致恬	Synaptotagmin III is abundantly expressed in rat retinal neurons to regulate retinal waves during the developmental critical period	-

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第八屆 (100年)

優秀論文獎得獎人

姓名	單位	指導教授	論文題目	學術刊物
劉祐禎	台灣大學生化科學研究所	李宗璘	Interception of teicoplanin oxidation intermediates yields new antimicrobial scaffolds.	Nature Chemical Biology 7: 304-309 (2011)
吳權娟	生物化學暨分子生物研究所	詹迺立	Structural Basis of Type II Topoisomerase Inhibition by the Anticancer Drug Etoposide.	Science 333(6041): 459-462 (2011)
林佑憲	國立陽明大學神經科學研究所	陳儀莊	Dysregulated brain-type creatine kinase is associated withhearing impairment in mice with Huntington's disease.	Journal of Clinical Investigation 121(4): 1519-1523 (2011)
朱自淳	陽明大學神經科學研究所	陳儀莊	Nuclear translocation of AMPK-a1 potentiates striatal neurodegeneration in Huntington's disease	Journal of Cell Biology 194(2): 209-227 (2011)
許信賢	陽明大學臨床醫學研究所	吳國瑞	Bmi 1 is essential in Twistl-induced epithelial-mesenchymal transition	Nature Cell Biology 12(10): 982-992 (2010)

壁報展示獎得獎人

姓名	單位	指導教授	論文題目	學術刊物
吳佩容	國立臺灣大學分子醫學研究所	陳瑞華	DAPK activates MARK1/2 to regulate microtubule assembly, neuronal differentiation, and tau toxicity	Cell Death and Differentiation 18(9): 1507-1520 (2011)
翁國峰	長庚大學生物醫學研究所	施信如	Enterovirus 71 3C Protease Cleaves a Novel Target CstF-64 and Inhibits Cellular Polyadenylation	PLos Pathogens 5(9): e1000593 (2009
李松柏	國防醫學院生命科學研究所所	阮麗蓉	Host-viral effects of chromatin assembly factor 1 interaction with HCMV IE2	Cell Research 21(8): 1230-1247 (2011)
周雅菁	台灣大學醫學院微生物所	蔡錦華	Requirement for LMP1-induced RON receptor tyrosine kinase in Epstein-Barr virus-mediated B cell proliferation	Blood 118(5): 1340-1349 (2011)
黃鵬年	長庚大學醫學生物研究所生物技術組	林昭吟	Far Upstream Element Binding Protein 1 Binds the Internal Ribosomal Entry Site of Enterovirus 71 and Enhances Viral Translation and Viral Growth	-

第七屆 (99年)

優秀論文獎得獎人

姓名	單位	指導教授	論文題目	學術刊物
林峰銘	國防醫學院生命科學所	王廷方	Yeast axial-element protein, Red1, binds SUMO chains to promote meiotic interhomologue recombination and chromosome synapsis	EMBO J. 29(3): 586-596 (2010)
周睿鈺	國立陽明大學生命科學系暨基因體科學研究所	呂俊毅	Multiple molecular mechanisms cause reproductive isolation between three yeast species	Plos Biology 8(7): e1000432 (2010)
呂國昀	陽明大學生理學研究所	李宗玄	Erythropoietin Suppresses the Formation of Macrophage Foam Cells : Role of Liver X Receptor α	Circulation 121: 1828-1837 (2010)

壁報展示獎得獎人

姓名	單位	指導教授	論文題目	學術刊物
李棟樑	中央研究院分子生物研究所	沈哲覦	JNK-Mediated Turn-over and Stabilization of the Transcription Factor p45/NF-E2 During Differentiation of Murine Erythroleukemia Cells	Proceedings of the National Academy of Sciences of the United States of America 107 (1): 52-57 (2010)
徐綜遠	台灣大學分子與細胞生物學研究所	吳益群	Engulfment of Apoptotic Cells in *C. elegans* Is Mediated by Integrin α/SRC Signaling	Current Biology 20(6): 477-486 (2010)
李國維	國防醫學院生命科學研究所	余叔美	Coordinated Responses to Oxygen and Sugar Deficiency Allow Rice Seedlings to Tolerate Flooding	Science Signaling 2(91): ra61 (2009)
游成州	台大醫學院生化暨分子生物學研究所	周綠蘋	Valosin-containing protein plays an important role in the protection of gastric epithelial cells from *Helicobacter pylori* -induced apoptosis through activation of AKT	-
廖辰芯	長庚大學生物醫學研究所	林光輝	Dickkopf 4 Positively Regulated by Thyroid Hormone Receptor Suppresses Cell Invasion in Human Hepatoma Cells	-
游舒涵	台大醫學院生化暨分子生物學研究所	周綠蘋	Phosphoproteomics Approach to Analyze Subcellular Localization Change of Phosphoproteins induced by Helicobacter Pylori	-

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第六屆 (98年)

優秀論文獎得獎人

姓名	單位	指導教授	論文題目	學術刊物
謝幸佳	國防醫學院生命科學研究所	司徒惠康	Transgenic expression of single-chain anti-CTLA-4 Fv on beta cells protects NOD mice from autoimmune diabetes	Journal of Immunology 183(4): 2277-85 (2009)
陳立強	長庚大學分子醫學研究中心	張玉生	Thymidine Phosphorylase is Regulated by hnRNP K-mediated mRNA Stability and is a Prognostic Marker for Nasopharyngeal Carcinoma	Oncogene 28, 1904–1915 (2009);Clinical Cancer Research 14, 3807–3813 (2008)
吳函蒼	陽明大學生物化學暨分子生物研究所	吳國瑞	Interaction between PHOX2B and CREBBP mediates synergistic activation: mechanistic implications of PHOX2B mutants	Human mutation 30(4): 655-660 (2009)
蔡淑君	台大醫學院微生物研究所	蔡錦華	EBV Zta protein induces the expression of interleukin-13, promoting the proliferation of EBV-infected B cells and lymphoblastoid cell lines	Blood 114(1): 109-118 (2009)

壁報展示獎得獎人

姓名	單位	指導教授	論文題目	學術刊物
賴琪婷	長庚大學生物醫學研究所生化分生組	陳華鍵	Study of ebv-mir-BART18-5p targets by proteomics approach	-

第五屆 (97年)

優秀論文獎得獎人

姓名	單位	指導教授	論文題目	學術刊物
李曉暉	台大醫學院生物化學暨分子生物學研究所	張智芬	Regulation of RhoA-dependent ROCKII activation by Shp2	Journal of Cell Biology 181(6): 999-1012 (2008)
鄭大山	高雄醫學大學醫學研究所	洪義人	Glycogen Synthase Kinase 3-beta Interacts with and Phosphorylates the Spindle-associated Protein Astrin	Journal of Biological Chemistry 283(4): 2454-2464 (2008)
陳嘉玲	成功大學基礎醫學研究所	林以行	Ceramide induces p38 MAPK and JNK activation through a mechanism involving a thioredoxin-interacting protein-mediated pathway	Blood 111(8): 4365-4374 (2008)
陳建村	國立陽明大學生化暨分子生物	魏耀揮	Coordinated Changes of Mitochondrial Biogenesis and Antioxidant Enzymes during Osteogenic Differentiation of Human Mesenchymal Stem Cells	Stem Cells 26(4): 960-968 (2008)

壁報展示獎得獎人

姓名	單位	指導教授	論文題目	學術刊物
陳淑怡	台灣國立中興大學生命科學系	陳鴻震	Direct interaction of focal adhesion kinase (FAK) with Met is required for FAK to promote hepatocyte growth factor-induced cell invasion	Molecular and Cellular Biology 26(13): 5155-5167 (2006)
黃琤	台大醫學院生化暨分生所	張明富	Large Hepatitis Delta Antigen Is a Novel Clathrin Adaptor-Like Protein	Journal of Virology 81(11): 5985-5994 (2007)
施景文	陽明大學生化分生所	吳妍華	Candidate tumor suppressor DDX3 RNA helicase specifically represses CAP-dependent translation by acting as an eIF4E inhibitory protein	Oncogene 27: 700-714 (2008)
張心儀	台灣大學分子與細胞生物學研究所	阮雪芬	Targeting therapy for breast carcinoma by ATP synthase inhibitor aurovertin B	Journal of Proteome Research 7(4): 1433-44 (2008)

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第四屆 (96年)

優秀論文獎得獎人

姓名	單位	指導教授	論文題目	學術刊物
白倩華	陽明大學生物化學所	林俊宏	Dual binding sites for translocation catalysis by Escherichia coli glutathionylspermidine synthetase	The EMBO Journal 25(24): 5970-5982 (2006)
蔡國旺	國防醫學院生科所	林文昌	Wobble Splicing Reveals the Role of the Branch Point Sequence-to-NAGNAG Region in 3' Tandem Splice Site Selection	Molecular and Cellular Biology 27(16): 5835-5848 (2007)

壁報展示獎得獎人

姓名	單位	指導教授	論文題目	學術刊物
林宜玫	國立成功大學基礎醫學研究所	孫孝芳	Functional polymorphisms of the human tryptophan hydroxylase 2 genes confer risk for bipolar disorder in Han Chinese	Archives of general psychiatry 64(9): 1015-1024 (2007)
余俊穎	台灣大學分子醫學研究所	周祖述	A bipartite signal regulates the faithful delivery of apical domain marker podocalyxin/gp135	Molecular Biology of the Cell 18(5): 1710-1722 (2007)
林怡彣	國防生命科學研究所/中研院生物醫學研究所	蕭百忍	Partial Duplication at AZFc on the Y Chromosome Is a Risk Factor for Impaired Spermatogenesis in Han Chinese in Taiwan	Human Mutation 28(5): 486-494 (2007)

第三屆 (95年)

優秀論文獎得獎人(博士)

姓名	單位	指導教授	論文題目	學術刊物
林明德	台灣大學分子與細胞生物學研究所	周子賓	Drosophila decapping protein 1, dDcp1, is a component of the oskar mRNP complex and directs its posterior localization in the oocyte	Developmental Cell 10(5): 601-613 (2006)
趙啟宏	陽明大學生化暨分子生物研究所	吳妍華	DDX3, a DEAE box RNA helicase with tumor growth-suppressive property and transcriptional regulation activity of the p21 promoter, is a candidate tumor suppressor	Cancer Research 66(13): 6579-6588 (2006)
張元貞	台灣大學生化分生所	張智芬	Contribution of Guanine Exchange Factor H1 in Phorbol Ester-Induced Apoptosis	Cell Death and Differentiation 13(12): 2023-2032 (2006)
徐于喬	陽明大學遺傳所	沈哲毅	Sumoylation of p45/NF-E2: Nuclear Positioning and Transcriptional Activation of the Mechanism beta-like Globin Gene Locus	Molecular and Cell Biology 25(23): 10365-10378 (2005)

優秀論文獎得獎人(碩士)

姓名	單位	指導教授	論文題目	學術刊物
蔡宏基	台灣大學微生物所	鄧述諄	Involvement of Topoisomerase III in Telomere-Telomere Recombination	Journal of Biological Chemistry 281: 13717-13723 (2006)
許雅涵	台灣大學微生物所	李財坤	Distribution of gyrase and topoisomerase IV on bacterial nucleoid: implication for nucleoid organization	Nucleic Acid Research 34(10): 3128-3138 (2006)

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第二屆 (94年)

優秀論文獎得獎人(博士)

姓名	單位	指導教授	論文題目	學術刊物
彭瑞銘	台大生化所	梁啟銘	VP1 of Foot-and-Mouth disease virus induces apoptosis via the Akt signaling pathway	Journal of Biological Chemistry 279: 521680174 (2005)
張哲菖	國防生科所	施修明	Daxx mediates the small ubiquitin-like modifier-dependent transcriptional repression of Smad4	Journal of Biological Chemistry 280(11): 10164-73 (2005)
石宗憲	成大基醫所	施桂月	Evidence of human thrombomodulin domain as a novel angiogenic factor	Circulation 111: 1627-36 (2005)

優秀論文獎得獎人(碩士)

姓名	單位	指導教授	論文題目	學術刊物
楊智勝	台大生化所	陳宏文	FBW2 targets GCMa to the ubiquitin-proteasome degradation system	Journal of Biological Chemistry 280(11): 10083-90 (2005)
朱自淳	慈濟神經科學所	楊定一	Protective effects of S-nitrosoglutathione against amyloid b-peptide neurotoxicity	Free Radical Biology and Medicine 38(7): 938-949 (2005)
王郁茜	師大生科系	王憶卿	Wild-type p53 overexpression and its correlation with MDM2 and P14arf alerations: An alternative pathway to non-small cell lung cancer	Journal of Clinical Oncology 23(1): 154-164 (2005)

第一屆 (93年)

優秀論文獎得獎人(博士)

姓名	單位	指導教授	論文題目	學術刊物
詹世鵬	陽明大學微免所	鄭淑珍	The Prp19p-Associated Complex in Spliceosome Activation	Science 302(5643): 279-82. (2003)
許志宏	清華大學分子與細胞生物所	張大慈	HCMV IE2-mediated inhibition of HAT activity downregulates p53 function	The EMBO Journal 23: 2269-2280 (2004)
殿展言	國防暨中研院國際研究生分子細胞生物學程	簡正鼎	Distinct protein degradation mechanisms mediated by Cul1 and Cul3 controlling Ci stability in Drosophila eye development	Genes and Development 16(18): 2403-14 (2002)

優秀論文獎得獎人(碩士)

姓名	單位	指導教授	論文題目	學術刊物
張光容	中央大學生命科學研究所	王健家	Translation initiation from a naturally occurring non-AUG codon in *Saccharomyces cerevisiae* .	Journal of Biological Chemistry 279(14): 133778-85 (2004)
羅嘉慧	台灣大學醫事技術學研究所	陶秘華	Antitumor and Antimetastatic Activity of IL-23	The Journal of Immunology 171: 600-607 (2003)

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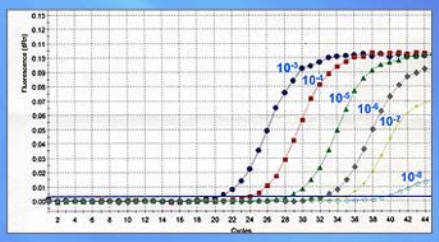

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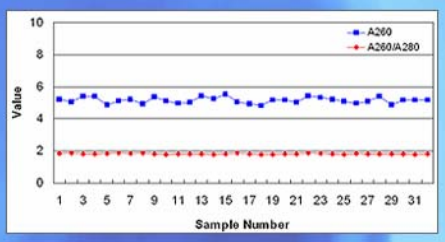

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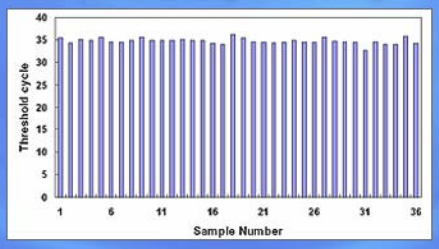

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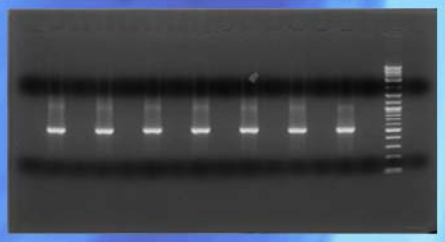

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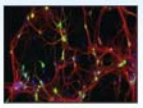

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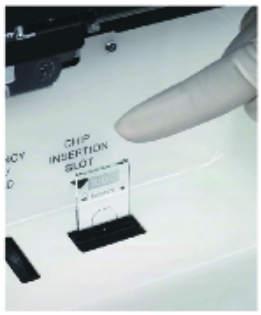

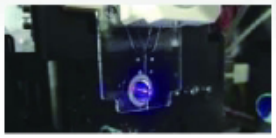
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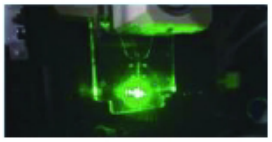
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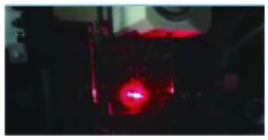
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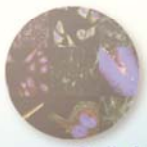
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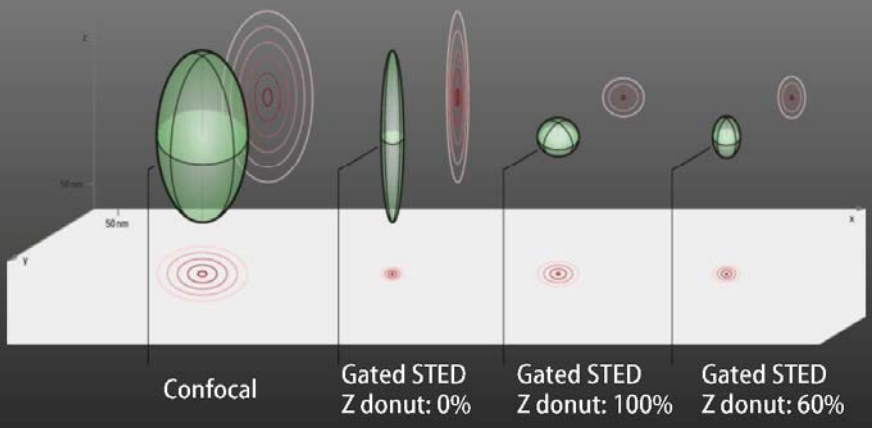

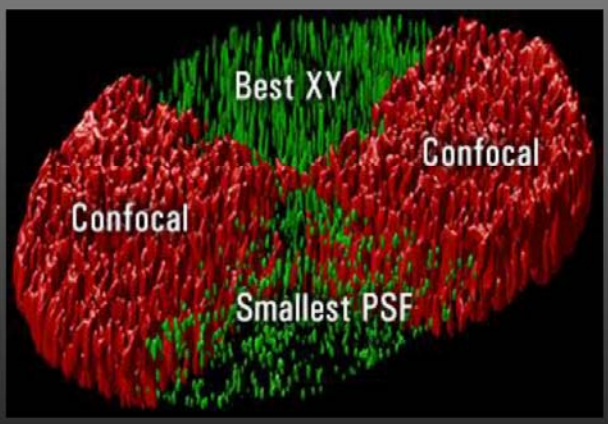

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Abberior -- 全球唯一專屬 Superresolution 專用螢光標定染劑

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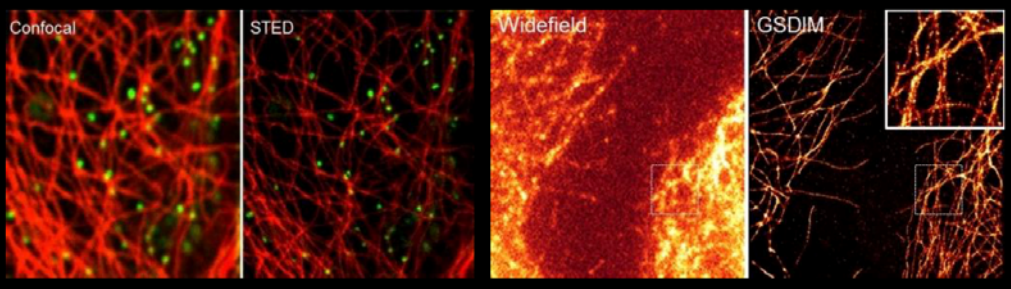
- Confocal microscopy
- Epifluorescence microscopy



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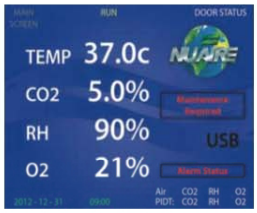
NUARE U.S.A.



彩色LCD液晶螢幕觸控操作，智慧面板人機互動
滅菌模式操作選擇：145℃乾式滅菌/95℃濕式滅菌
CO2 O2多種氣體運用，數位IR紅外線CO2 O2感測器
高效率過濾網/氣體濾膜ISO Class 5 FDA 認證
低溫培養可選擇原廠內建冷卻循環線圈裝置
機器曾遇斷電再復電時，會提示告知使用者
CO2 O2濃度測定儀 / CO2 O2濃度測定液

-86℃ 超低溫冷凍櫃 728/668/483 公升

微電腦控制面板、觸控式溫度設定操作
保固四年、壓縮機有延遲啟動保護功能
設定高溫/低溫警報、聲響及燈號告知
真空洩壓閥裝置、關門後仍可輕易開啟
可拆式雙內門、鷹嘴式門扣, 密閉緊實
全時系統自我診斷偵測、錯誤訊息顯示告知

生物安全櫃 寬度 3, 4, 5, 6呎

NSF登錄合格認證員, 提供確效、檢測、驗證、TAF報告書

TYPE A2
30%排出 70%循環
NU-425 NU-475
NU-437 NU-477
NU-440 NU-480

＊結構：內部及外部均為不鏽鋼304製，認證NSF/ANSI 49 EN12469
＊機身主體外殼之兩側與背部無烤漆或塗裝材料,為原不銹鋼材製作完成
＊風扇馬達及UV燈之開關與指示燈，可由控制面板及拉門分別控制啟閉
＊專利設計之袋狀高效率過濾網連結零洩漏氣流系統
＊DC ECM 直流變頻馬達，效率佳、節省能源、最新科技運用

TYPE B1
70% 排出 30%循環
NU-427

TYPE B2 100%排出
NU-430
NU-435

＊微電腦自動控制風速、彩色LCD液晶螢幕觸控操作
＊數位顯示 Downflow風速及Exhaust風量
＊顯示日期、時間、待機、運轉、馬達、UV燈之使用時數
＊圖樣指示狀態、聲響、視覺及錯誤指示告知，靜音裝置
＊所有參數資料設定具有密碼鎖定、校正功能
＊拉門高度過高或安全櫃內氣流不穩定時,聲響及視覺警告保護操作者
＊數位氣流感應器，監控濾網承載、電壓與環境因素自動遞補調整風速

動物處理用生物安全櫃 NU-677/NU-629

TYPE A2
30%排出70%循環
NU-677
NU-629

＊NSF 49 安全認證 ＊ DC ECM直流變頻馬達
＊專利設計高效率過濾網連結零洩漏氣流系統
＊預濾片補集毛髮皮屑 ＊活動腳輪或調水平腳選擇
＊電動升降調整工作高度，人員或座或站時，舒適操作

動物墊料處理台 NU-607

＊Class 1工作區完全負壓
＊過濾網99.99% 0.3 micron、活性碳濾網
＊工作區拉門全開高53公分、大鼠盒進出
＊可選用大或小鼠用墊料槽口單槽或雙槽

鼠盒更換操作台 NU-619

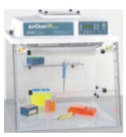
＊Push-Pull Airflow System裝置
＊雙風扇馬達進/排氣風量自動補償
＊電動升降調整工作高度
＊人員或座或站時，舒適操作

AirClean U.S.A.

免風管式

化學工作台

抽氣排煙櫃



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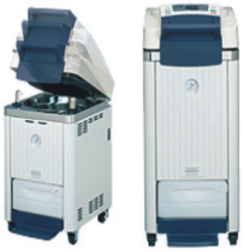
AirSafe™
可選擇設定氣流自動或手動模式
依實驗需求, 多種黏結碳濾網種類選擇

UVTect™
微電腦處理控制器觸控式
即時的顯示氣流監控,工作區確保潔淨

TOMY JAPAN

高壓滅菌鍋
44/58/79公升



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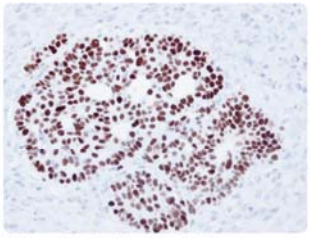
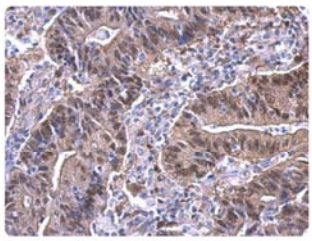
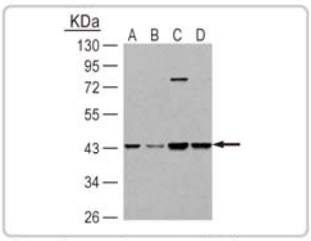


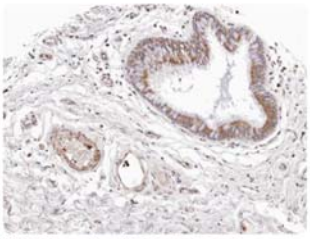
P53 antibody (GTX102965)
IHC analysis of paraffin-embedded Cal27 xenograft.



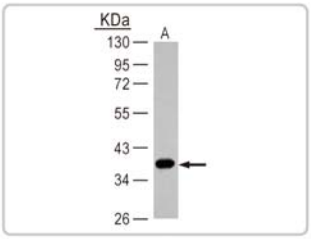
YAP1 antibody (GTX129151)
IHC analysis of paraffin-embedded colon carcinoma.



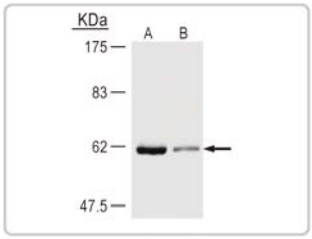
Glutamine synthetase antibody (GTX109121)
WB analysis of whole cell lysate. (A) U87MG. (B) SK-N-SH. (C) IMR32. (D) SK-N-AS.



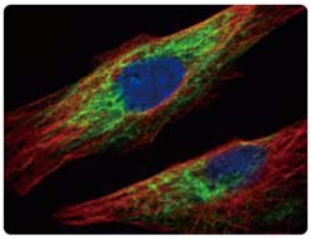
WNT11 antibody (GTX105971)
IHC analysis of paraffin-embedded lung SCC xenograft.



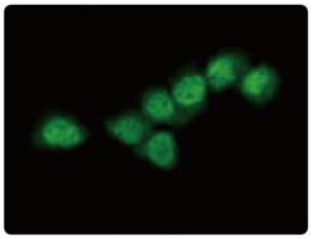
Arginase 1 antibody (GTX109242)
WB analysis of HepG2 whole cell lysate.



SQSTM1 antibody [N3C1], Internal (GTX100685)
WB analysis of Huh7 whole cell lysate. (A) Untreated. (B) Thapsigargin treatment.



HDAC6 antibody [N1], N-term (GTX100722)
ICC/ IF analysis of HeLa cells.



QK1 antibody [N2C3] (GTX115969)
ICC/ IF analysis of A431 cells.

With GeneTex Quality Antibodies on

Cat. No.	Product name	Publication information
GTX627408	GAPDH antibody	**Nat Genet.** 2014 May 4 (Epub ahead)
GTX103323	T-Plastin antibody	**N Engl J Med.** 2013 Oct 17;369(16):1529-36
GTX119426	SNX18 antibody	**Nature.** 2013 Jul 11;499(7457):233-7
GTX104255	GOLGA5 antibody [N2C2], Internal	**Nat Cell Biol.** 2013 Dec;15(12):1473-85
GTX112112	GRASP65 antibody [N1C1]	**Nat Cell Biol.** 2013 Dec;15(12):1473-85
GTX101468	PDI antibody [N1N3]	**Cell.** 2013 Jun 20;153(7):1494-509
GTX104768	VPS29 antibody [C1C3]	**Cell.** 2013 Feb 28;152(5):1051-64
GTX111593	PI 3 Kinase p85 beta antibody [N3C3]	**Nat Cell Biol.** 2013 May;15(5):472-80
GTX115305	SETDB1 antibody [N1], N-term	**Nat Genet.** 2013 Jan;45(1):34-42
GTX119726	Pygopus 2 antibody	**Nature.** 2013 Aug 29;500(7464):598-602
GTX129571	TSLP antibody	**Cell.** 2013 Oct 10;155(2):285-95
GTX100664	MUC2 antibody [C3], C-term	**Nature.** 2012 Nov 8;491(7423):254-8
GTX101661	AMPK gamma 1 antibody	**Nature.** 2012 Feb 8;482(7384):251-5
GTX103487	AMPK alpha 2 antibody	**Nature.** 2012 Feb 8;482(7384):251-5
GTX104507	JAM-B antibody	**Nature.** 2012 Nov 8;491(7423):254-8
GTX106751	UVSSA antibody	**Nat Genet.** 2012 May;44(5):593-7
GTX109519	MAD1 antibody	**Nat Cell Biol.** 2012 May 13;14(6):593-603
GTX114178	AMPK gamma 2 antibody [C2C3], C-term	**Nature.** 2012 Feb 8;482(7384):251-5
GTX121453	TET3 antibody [C3], C-term	**Cell.** 2012 Dec 7;151(6):1200-13
GTX100145	ERCC8 antibody [N2C2], Internal	**Cell.** 2011 Nov 23;147(5):1024-39
GTX101277	HMGB1 antibody	**Nature.** 2011 Oct 16;479(7371):117-21
GTX107678	NFkB p65 antibody	**Nat Genet.** 2011 Mar;43(3):253-8
GTX109669	Calnexin antibody [C3], C-term	**Cell.** 2011 Sep 30;147(1):173-84
GTX105661	Bcl-X antibody	**Cell.** 2010 Aug 20;142(4):625-36

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實現

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- 獲得無與倫比的可靠性和再現性

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